DOI: 10.1002/ejoc.201000795

Synthesis of 2-, 3-, and 4-Substituted Pyrido[2,3-*b*]indoles by C–N, C–O, and C–C(sp) Bond Formation

Cédric Schneider,[a] David Goyard,[a] David Gueyrard,[a] Benoît Joseph,[b] and Peter G. Goekjian*[a]

Keywords: Natural products / Nitrogen heterocycles / Palladium / Polycycles / Cross-coupling

The synthesis of 2-, 3-, and 4-substituted α-carbolines is described starting from the corresponding chloropyrido[2,3-*b*]-indoles by Buchwald–Hartwig and Sonogashira cross-coupling reactions. Regioselective Sonogashira reactions on 2,4-dichloropyrido[2,3-*b*]indoles are also presented as an efficient route to unsymmetrically 2,4-disubstituted α-carbolines.

Introduction

α-Carbolines (pyrido[2,3-*b*]indoles) display a variety of biological properties.[1] Among them, natural products such as Grossularine-1 and -2 (Figure 1), which are marine alkaloids isolated from *Dendrodoa grossularia* in 1989, have attracted interest for their antiproliferative activity.[2] Similarly, Mescengricin, which was isolated from *Streptomyces griseoflavus*, was found to protect neuronal cells by suppressing the excitotoxicity induced by L-glutamate (Figure 1).[3] At the same time, a rapidly increasing number of synthetic pyrido[2,3-*b*]indoles have appeared in the patent literature for a range of potential applications.[4] Thus, much effort has been devoted to the synthesis and functionalization of pyrido[2,3-*b*]indoles.[5]

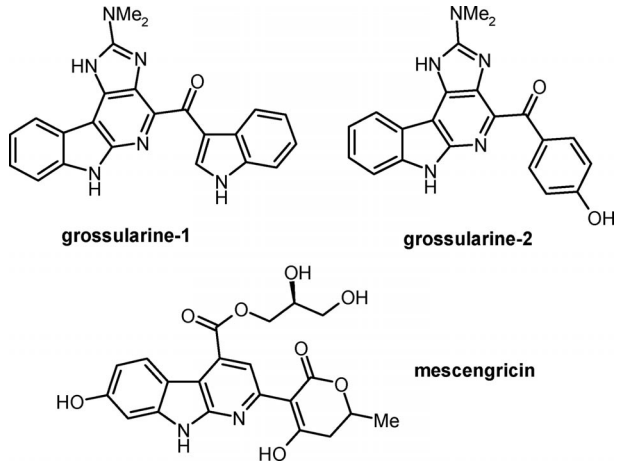


Figure 1. α-Carboline natural products.

The synthesis of heteroatom-substituted α-carbolines, such as the grossularines or compounds **I** and **II**, having potent cyclin-dependent kinase (CDK) inhibitory activities[4a,4b] (Figure 2), has attracted our attention in particular. Relatively few methods are available for preparing heteroatom-substituted α-carbolines. For the most part, heteroatoms have been introduced either prior to formation of the α-carboline skeletons,[6] starting from 2-acetamidino-3-cyanoindoles, 2-amidinylindole-3-carbaldehyde, or 4-amino-2-(benzotriazol-1-yl)quinolines, or by functionalization of halo- or *O*-triflate-substituted pyridines by nucleophilic substitution.[4a,4b,7] The introduction of alkylamines by palladium-catalyzed coupling reaction has been reported briefly by Panunzio et al.[5h] Similarly, we became interested in alkynyl-substituted pyrido[2,3-*b*]indoles, which have re-

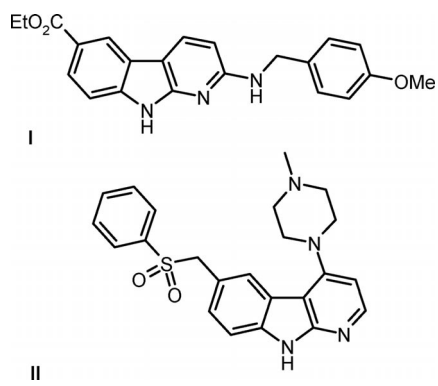
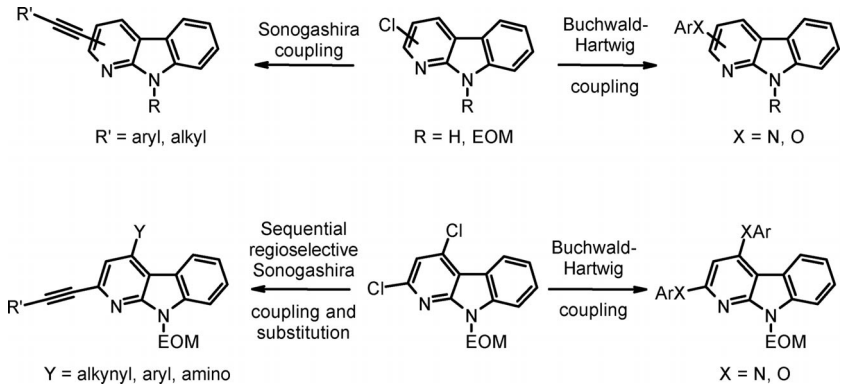


Figure 2. α-Carboline CDK inhibitors.

[a] Université de Lyon, Laboratoire de Chimie Organique 2-Glycochimie, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, UMR 5246 CNRS – Université Claude Bernard Lyon 1, Bât. Curien CPE-Lyon, 43 bd du 11 novembre 1918, 69622 Villeurbanne, France
Fax: +33-4-72448349
E-mail: goekjian@univ-lyon1.fr
[b] Université de Lyon, Université Claude Bernard – Lyon 1, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires UMR-CNRS 5246, Bât. Curien CPE-Lyon, 43 bd du 11 novembre 1918, 69622 Villeurbanne, France

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000795.



Scheme 1. Functionalization of α-carbolines at positions 2, 3, and 4.

ceived scant attention, with only an isolated example of the Sonogashira coupling on 3-bromo-α-carbolines being described by Sennhenn et al. in the patent literature.[4b] We therefore decided to study the preparation of heteroatom- and alkynyl-substituted α-carbolines from chlorine-substituted precursors using palladium chemistry.

Palladium-catalyzed Buchwald–Hartwig,[8] and Sonogashira coupling reactions[9] and, in particular, sequential double coupling reactions on readily available chloro- or dichloro-α-carbolines would provide a particularly efficient approach to a wide range of heteroatom-substituted compounds, especially those involving relatively less nucleophilic substituents, such as arylamino and aryloxy groups. We also noted that the preparation of alkynyl-substituted α-carbolines from the corresponding chloropyrido[2,3-*b*]-indoles had not been reported and we thus investigated Sonogashira coupling reactions on this system. Whereas such reactions can now be considered as classical organic reactions, many different experimental conditions have been reported, thus the most appropriate conditions must be identified for each particular heterocycle (Scheme 1). Furthermore, sequential double-coupling reactions provide a particularly efficient approach to more highly substituted compounds, and we recently reported a sequential double Suzuki coupling reaction on 2,6-, 3,6-, and 4,6-bromo,chloropyrido[2,3-*b*]indoles.[10] We report here the results of our investigations into the sequential double Sonogashira coupling reaction on the more challenging case, 2,4-dichloropyrido[2,3-*b*]indole.

Results and Discussion

Synthesis of Monosubstituted α-Carbolines

The readily accessible chloropyrido[2,3-*b*]indoles **1**–**3** were selected as initial starting materials for the study of palladium-catalyzed C–N, C–O, and C–C(sp) bond formation on the α-carboline ring system. The 2- and 3-chloropyrido[2,3-*b*]indoles **1** and **2** were prepared in two steps using a Graebe–Ullmann reaction starting from the corresponding dichloropyridines,[5e,11] and the 4-chloropyrido-[2,3-*b*]indole **3** was synthesized through a Reissert–Henze reaction on pyrido[2,3-*b*]indole *N*-oxide.[12] The ethoxymethyl-protected forms **4**–**6** (Figure 3) were prepared by *N*-alkylation with ethoxymethyl chloride (EOMCl) in the presence of sodium hydride in *N*,*N*-dimethylformamide (DMF).

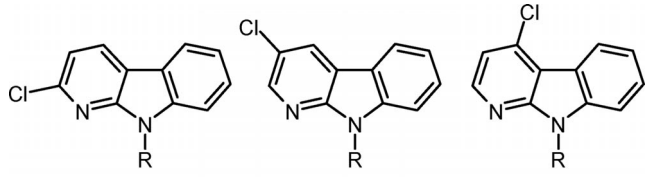


Figure 3. Chloropyrido[2,3-*b*]indole starting materials.

Various parameters were investigated with 2-chloropyrido[2,3-*b*]indole (**1**) as substrate (Table 1, entries 1–6). Buchwald[13] and Thutewohl[14] demonstrated recently that C–N and C–O coupling reactions can be performed on chloro-substituted pyridines and 7-azaindoles using $[Pd_2(dba)_3]$

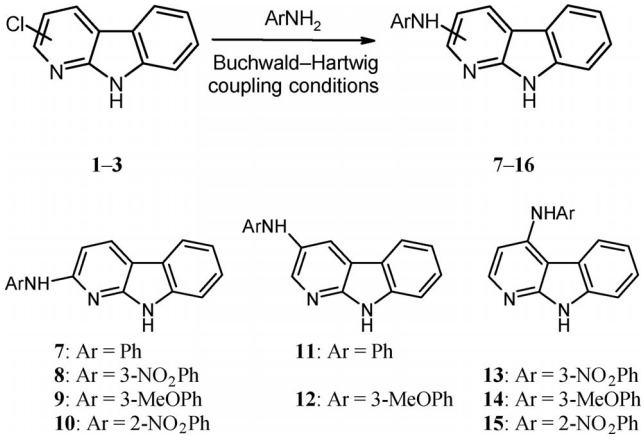
Table 1. Buchwald–Hartwig coupling reactions on 2-, 3-, and 4-chloropyrido[2,3-*b*]indoles with arylamines.

Entry	Starting material	Ar	Conditions[a]	Product	Yield [%]
1	**1**	Ph	A	**7**	0
2	**1**	Ph	B	**7**	62
3	**1**	3-$NO_2C_6H_4$	B	**8**	0
4	**1**	3-$NO_2C_6H_4$	C	**8**	61
5	**1**	3-$MeOC_6H_4$	C	**9**	70
6	**1**	2-$NO_2C_6H_4$	C	**10**	53
7	**2**	Ph	C	**11**	0
8	**2**	Ph	D	**11**	78
9	**2**	3-$MeOC_6H_4$	D	**12**	80
10	**3**	3-$NO_2C_6H_4$	C	**13**	79
11	**3**	3-$MeOC_6H_4$	C	**14**	70
12	**3**	2-$NO_2C_6H_4$	C	**15**	80

[a] Method A: $[Pd_2(dba)_3]$ (0.08 equiv.), X-Phos (0.16 equiv.), NaO*t*Bu (3 equiv.), amine (1.3 equiv.), toluene, 110 °C, 12 h; Method B: $[Pd_2(dba)_3]$ (0.08 equiv.), X-Phos (0.16 equiv.), LiHMDS (3 equiv.), arylamine (1.3 equiv.), THF, 70 °C, 12 h; Method C: $[Pd_2(dba)_3]$ (0.08 equiv.), X-Phos (0.16 equiv.), K_2CO_3 (3 equiv.), arylamine (1.3 equiv.), *t*BuOH, 100 °C, 12 h; Method D: $[Pd_2(dba)_3]$ (0.08 equiv.), X-Phos (0.16 equiv.), NaO*t*Bu (3 equiv.), arylamine (1.3 equiv.), *t*BuOH, 100 °C, 12 h.

and X-Phos. Using this catalytic system, the influence of the solvent [toluene, tetrahydrofuran (THF) or *tert*-butyl alcohol (*t*BuOH)] and the base (LiHMDS, K_2CO_3 or NaO*t*Bu) was studied to optimize the reaction on the α-carboline substrate. The Buchwald [$Pd_2(dba)_3$]/X-Phos catalytic system was found to be effective, however, the solvent and base still needed to be adapted to the particular nucleophile. The conditions described by Thutewohl were found to be the most general. The moderate yields reflect, in part, difficulties in the isolation and purification of the poorly soluble products.

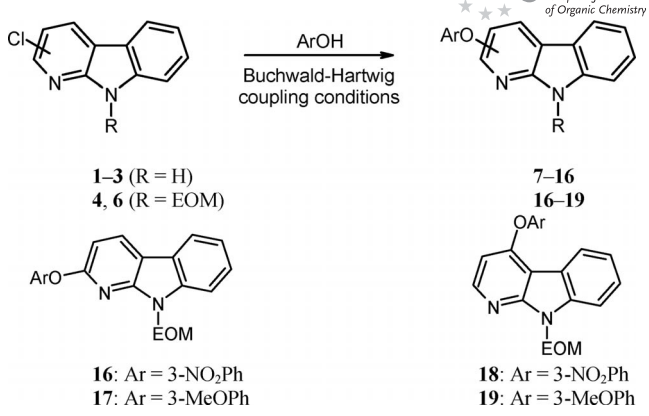
2- and 4-chloro-substituted α-carbolines **1** and **3** were thus coupled cleanly with aniline, 3-nitroaniline, 3-methoxyaniline, and 2-nitroaniline in 53–80% yields using Thutewohl's conditions (Table 1, entries 2–6 and 10–12). It should be noted that no coupling was observed in these cases under basic conditions in the absence of palladium catalyst. However, the conditions proved unsuccessful for the less reactive 3-chloro-isomer **2** (Table 1, entry 7). Use of the stronger base, NaO*t*Bu in *t*BuOH, proved to be far superior. This method allowed clean coupling of aniline and 3-methoxyaniline in 78 and 80% yield, respectively (Table 1, entries 8 and 9). However, electron-deficient anilines, such as 3-nitroaniline, failed to provide the desired 3-substituted products under any of the conditions tested (Scheme 2).



Scheme 2. Synthesis of 2-, 3-, and 4-arylamino-α-carbolines.

Having successfully achieved the coupling of arylamines to the α-carboline ring system, we investigated the Buchwald–Hartwig coupling of the corresponding phenols. Initial attempts with the unprotected chloropyrido[2,3-*b*]-indoles **1**–**3** proved unsuccessful. However, it has previously been shown that protection of the nitrogen is important to avoid deactivation of the aryl chlorides under basic conditions.[14,15] Therefore, coupling of the EOM-protected chloropyrido[2,3-*b*]indoles **4**–**6** were investigated (Scheme 3).

The coupling of both electron-rich and -deficient phenols proceeded smoothly with the protected 2- and 4-chloropyrido[2,3-*b*]indoles **4** and **6** under Buchwald's conditions in toluene in the presence of NaO*t*Bu (Table 2). The yields were acceptable, ranging from 62 to 86%. However, we were unable to couple the protected 3-chloropyrido[2,3-*b*]indole **5** under any of the conditions investigated.



Scheme 3. Synthesis of 2- and 4-aryloxy-α-carbolines.

Table 2. Buchwald–Hartwig coupling reactions of 2- and 4-chloropyrido[2,3-*b*]indoles with phenols.[a]

Entry	Starting material	Ar	Product	Yield [%]
1	**4**	3-NO$_2$C$_6$H$_4$	**16**	62
2	**4**	3-MeOC$_6$H$_4$	**17**	67
3	**6**	3-NO$_2$C$_6$H$_4$	**18**	86
4	**6**	3-MeOC$_6$H$_4$	**19**	78

[a] Reagents and conditions: [$Pd_2(dba)_3$] (0.08 equiv.), X-Phos (0.16 equiv.), NaO*t*Bu (3 equiv.), phenol (1.3 equiv.), toluene, 110 °C, 12 h.

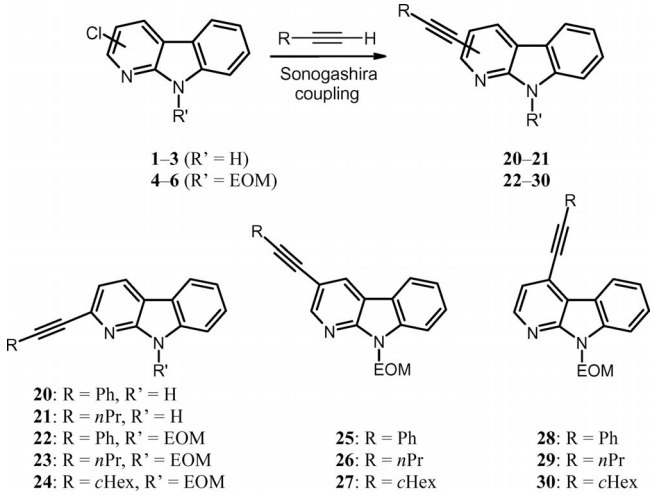
Having performed the Buchwald–Hartwig coupling reactions on either protected or unprotected α-carbolines, we next turned our attention to the Sonogashira reaction (Table 3 and Scheme 4). The coupling reaction to be proved effective with the unprotected 2-chloropyrido[2,3-*b*]indole (**1**), using either aryl- or alkyl-substituted acetylenes, and gave the desired products in moderate 61–64% yields (Table 3, entries 1 and 2). The copper-free conditions used by Buchwald in the pyridine cases, in aprotic solvents (dioxane or acetonitrile) with an inorganic base (Cs_2CO_3) proved to be the most effective.[16] However, the poor solubility of the substrates **1**–**3** in these solvents limited the applicability of these conditions. The reaction was therefore investigated using the EOM-protected chloropyrido[2,3-*b*]indoles **4**–**6**. The coupling reaction proceeded in high yields on the 2-, 3-, and 4-chloropyrido[2,3-*b*]indoles (Table 3, entries 3–11),

Table 3. Sonogashira coupling reactions of 2-, 3-, and 4-chloropyrido[2,3-*b*]indoles with acetylenes.[a]

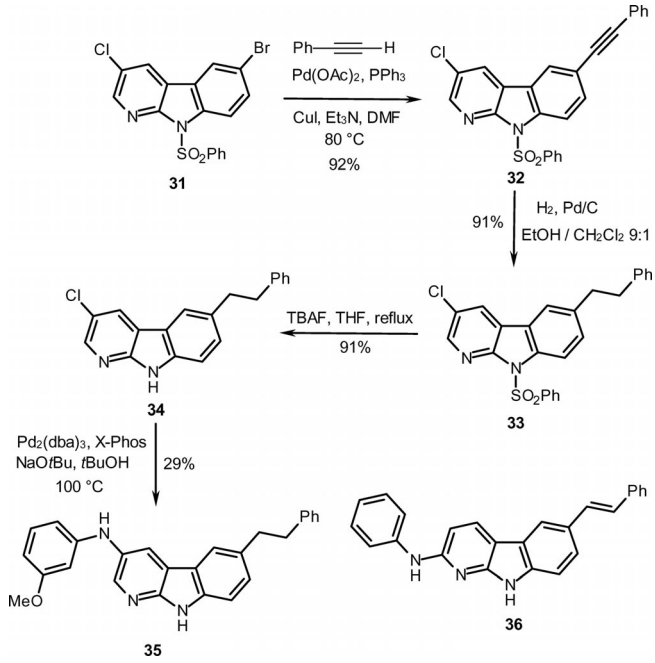
Entry	Starting material	R	*T* [°C]	*t* [h]	Product	Yield [%]
1	**1**	Ph	70	12	**20**	64
2	**1**	*n*Pr	70	12	**21**	61
3	**4**	Ph	90	12	**22**	80
4	**4**	*n*Pr	70	12	**23**	85
5	**4**	*c*Hex	70	12	**24**	87
6	**5**	Ph	90	12	**25**	95
7	**5**	*n*Pr	70	12	**26**	81
8	**5**	*c*Hex	90	24	**27**	63
9	**6**	Ph	90	12	**28**	95
10	**6**	*n*Pr	70	12	**29**	90
11	**6**	*c*Hex	90	12	**30**	80

[a] Reagents and conditions: [$PdCl_2(MeCN)_2$] (0.08 equiv.), X-Phos (0.16 equiv.), Cs_2CO_3 (2.6 equiv.), acetylene (1.3 equiv.), MeCN.

although slightly higher temperatures and longer reaction times were required with the less reactive acetylenes (e.g., Table 3, entry 8).



Scheme 4. Synthesis of 2-, 3-, and 4-ethynyl-α-carbolines.

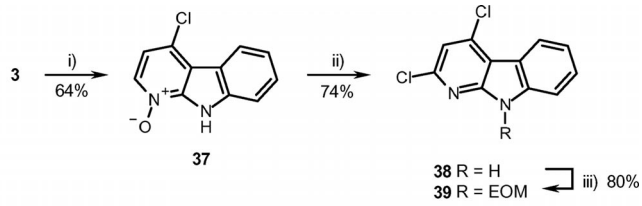


Scheme 5. Sequential palladium-catalyzed coupling reactions of 6-bromo-3-chloropyrido[2,3-*b*]indole **31**.

Synthesis of Disubstituted α-Carbolines by Simultaneous or Sequential Double Coupling Reactions

The ability to perform either one-pot, double-coupling reactions, or regioselective sequential bis-coupling reactions provides extremely rapid and efficient access to a large variety of structurally diverse heterocyclic compounds. The sequential double substitution reaction of 6-bromo-3-chloropyrido[2,3-*b*]indole (**31**), as demonstrated previously with the Suzuki coupling,[10] unsurprisingly, also worked in the case of a sequential Sonogashira–Buchwald–Hartwig coupling (Scheme 5). However, it was preferable to reduce the acetylene before performing the Buchwald–Hartwig coupling. Similarly, the more closely matched 6-bromo-2-chloropyrido[2,3-*b*]indole can be functionalized through a regioselective, sequential Suzuki–Buchwald–Hartwig coupling to furnish the compound **36**.

We therefore investigated the most challenging case, the bis-coupling reactions of 2,4-dichloropyrido[2,3-*b*]indoles **38** and **39** bearing two activated chlorine atoms of similar reactivity. These compounds were prepared through a second Reissert–Henze reaction on 4-chloropyrido[2,3-*b*]indole *N*-oxide (**37**; Scheme 6).



i) *m*CPBA (1.5 equiv.), $CHCl_3$, r.t., 12 h; ii) $MeSO_2Cl$ (2 equiv.), DMF, 100 °C, 12 h; iii) NaH (1.5 equiv.), EOMCl (2 equiv.), DMF, r.t., 12 h.

Scheme 6. Synthesis of 2,4-dichloropyrido[2,3-*b*]indoles.

We first investigated the double coupling reaction as a route to symmetrically 2,4-disubstituted α-carbolines (Table 4, entries 1–3). The double Buchwald coupling with 3-methoxyaniline proceeded smoothly by using the unprotected starting material **38** to provide the disubstituted product **40** in 90% yield. As in the monosubstituted cases, substitution with phenols and acetylenes was more effective on the EOM-protected 2,4-dichloropyrido[2,3-*b*]indole **39**, providing the 2,4-bis(methoxyphenyloxy)- and 2,4-bis(phenylethynyl)-substituted α-carbolines **41** and **42**, respectively (Table 4, entries 2 and 3) in acceptable yields (Scheme 7).

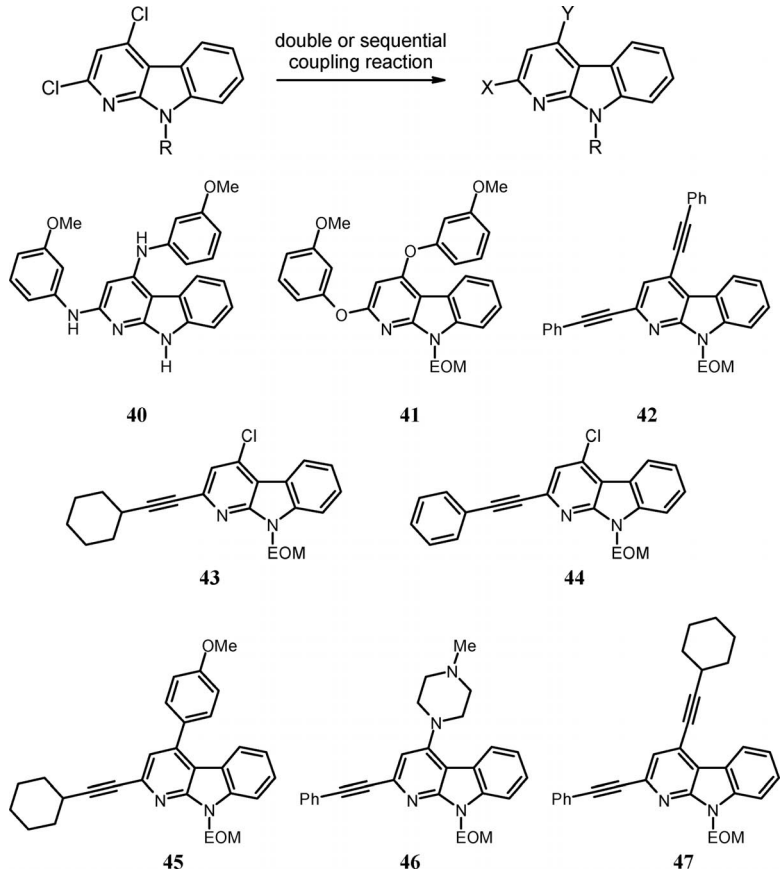
The regioselective monosubstitution of the 2,4-dichloropyrido[2,3-*b*]indole (**39**) based on a differential reactivity of the two activated chlorides would provide particularly efficient access to more complex α-carbolines. The Sonogashira reaction was used to test this hypothesis.[17] Using copper in the presence of $[PdCl_2(PPh_3)_2]$ and triethylamine, in a method first reported by Rault et al.,[18] proved effective, but the poor solubility of the starting material required the use of DMF as a co-solvent in our case. The reaction provided the monosubstituted acetylenes **43** and **44** with very good regiocontrol, although competing homodimerization of the acetylene required an optimization of the number of equivalents of acetylene in each case (Table 4, entries 4 and 5).

Having accessed the key monosubstituted α-carbolines **43** and **44**, a second substitution could be performed by applying subsequent Suzuki coupling (Table 4, entry 6), microwave-induced nucleophilic substitution (Table 4, entry 7), or Sonogashira coupling (Table 4, entry 8). As shown above, the Buchwald couplings could be used after reduction of the triple bond.

Table 4. Buchwald–Hartwig and Sonogashira coupling reactions of 2,4-dichloropyrido[2,3-*b*]indoles.

Entry	SM	X	Y	Method[a]	Cat. (equiv.)	Phosphane (equiv.)	Base (equiv.)	Solvent	*T* [°C]	*t* [h]	Product	Yield [%]
1	**38**	3-MeOPhNH	3-MeOPhNH	A	$Pd_2(dba)_3$ (0.08)	X-Phos (0.16)	K_2CO_3 (3)	*t*BuOH	100	12	**40**	90
2	**39**	3-MeOPhO	3-MeOPhO	B	$Pd_2(dba)_3$ (0.08)	X-Phos (0.16)	K_2CO_3 (3)	toluene	100	12	**41**	80
3	**39**	Ph-C≡C	Ph-C≡C	C	$Pd(Cl)_2(MeCN)_2$ (0.08)	X-Phos (0.16)	Cs_2CO_3 (5.2)	MeCN	90	12	**42**	62
4	**39**	*c*HexC≡C	Cl	D	$Pd(Cl)_2(PPh_3)_2$ (0.1) CuI (0.2)	PPh_3 (0.1)	Et_3N/DMF (2:1)		80	12	**43**	73
5	**39**	Ph-C≡C	Cl	D	$Pd(Cl)_2(PPh_3)_2$ (0.1) CuI (0.2)	PPh_3 (0.1)	Et_3N/DMF (2:1)		100	12	**44**	65
6	**43**	*c*HexC≡C	4-MeOPh	E	$Pd(PPh_3)_4$ (0.08)		K_2CO_3 (3)	H_2O/1,4-dioxane	100	12	**45**	71
7	**44**	Ph-C≡C	*N*-Me-piperazinyl	F					200	1	**46**	84
8	**44**	Ph-C≡C	*c*Hex-C≡C	G	$Pd(Cl)_2(PPh_3)_2$ (0.1) CuI (0.2)	PPh_3 (0.1)	Et_3N/DMF (2:1)		80	12	**47**	76

[a] Method A: 3-methoxyaniline (2.6 equiv.); Method B: 3-methoxyphenol (2.6 equiv.); Method C: phenylacetylene (2.6 equiv.); Method D: acetylene (2.5–3 equiv.); Method E: 4-methoxyphenylboronic acid (1.3 equiv.); Method F: microwaves, *N*-methylpiperazine; Method G: cyclohexylacetylene (3 equiv.).



Scheme 7. Sequential Sonogashira and Buchwald–Hartwig reactions of 2,4-dichloropyrido[2,3-*b*]indoles.

Conclusions

Palladium-catalyzed Buchwald–Hartwig and Sonogashira coupling reactions on readily accessible chloropyrido[2,3-*b*]indoles provide efficient and general access to nitrogen-, oxygen-, and carbon-substituted α-carbolines. In addition, the selective monosubstitution of 2,4-dichloropyrido[2,3-*b*]indoles followed by a second substitution reaction provides a particularly efficient route to complex compounds that may serve, for example, in the context of the parallel synthesis of biologically relevant molecules.

Experimental Section

General: All reactions were carried out under an argon atmosphere. Solvents (THF, *t*BuOH, toluene, acetonitrile, and DMF) and triethylamine were distilled and dried by standard methods. [$Pd_2(dba)_3$] was purchased from Strem chemicals, X-Phos [2-(dicyclohexylphosphanyl)-2′,4′,6′-triisopropylbiphenyl] and [$PdCl_2(PPh_3)_2$] were purchased from Aldrich. Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254}. Purifications on flash silica gel column chromatography were performed with Geduran silica gel Si 60 (40–63 μm). ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance DRX300 spectrometer at

25 °C. The following abbreviations are used to describe the observed multiplicities: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), triplet of doublets (td), multiplet (m), broad singlet (br. s), sextuplet (sext). ^{13}C NMR multiplicities were assigned on the basis of DEPT experiments. MS (EI, ESI, SIMS, LSIMS, and CI) and HRMS were recorded in positive ion mode with a Thermofinnigan apparatus. In the case of chlorine-containing compounds, the ^{35}Cl and ^{37}Cl isotope peaks are reported. IR spectra were recorded by attenuated-total-reflection (ATR) spectroscopy using a ZnSe crystal.

General Procedure for EOM Protection: NaH (60% in oil, 3 equiv.) was added to a stirred suspension of chloro-9*H*-pyrido[2,3-*b*]indole (1 equiv., 0.4 M in DMF) at 0 °C. After stirring at 0 °C for 20 min, EOM-Cl (2.5 equiv.) was added dropwise. The reaction mixture was stirred for 12 h and then poured into 5% aqueous saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure.

2-Chloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (4): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 1:1) to afford compound **4** (255 mg, 99% yield) as a white solid; m.p. 70–72 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3055, 2979, 2930, 2890, 1587, 1560, 1470, 1418, 1388, 1122, 1092, 1070, 1050, 911, 804, 773 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, J = 7.9 Hz, 1 H), 7.99 (d, J = 7.7 Hz, 1 H), 7.64 (d, J = 8.3 Hz, 1 H), 7.53 (td, J = 8.3, 7.3, 1.0 Hz, 1 H), 7.33 (td, J = 7.7, 1.0 Hz, 1 H), 7.18 (d, J = 7.9 Hz, 1 H), 5.92 (s, 2 H), 3.54 (q, J = 6.9 Hz, 2 H), 1.15 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2 (C), 147.6 (C), 139.4 (C), 130.4 (CH), 127.2 (CH), 121.3 (CH), 120.8 (CH), 120.4 (C), 115.8 (CH), 114.6 (C), 110.8 (CH), 71.1 (CH_2), 64.4 (CH_2), 15.0 (CH_3) ppm. MS (CI): m/z = 261, 263 [M + H^+]. HRMS (CI): calcd. for $C_{14}H_{14}ClN_2O$ 261.0795; found 261.0793.

3-Chloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (5): The product was purified by column chromatography on silica gel (CH_2Cl_2) to afford compound **5** (650 mg, 82% yield) as a white solid; m.p. 88–90 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3056, 2978, 2878, 1588, 1565, 1489, 1466, 1455, 1372, 1267, 1092, 1055, 1012, 902, 829, 781 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, J = 2.3 Hz, 1 H), 8.28 (d, J = 2.3 Hz, 1 H), 8.03 (d, J = 7.7 Hz, 1 H), 7.62 (d, J = 8.3 Hz, 1 H), 7.56 (td, J = 7.5, 7.1, 1.1 Hz, 1 H), 7.34 (td, J = 8.1, 1.1 Hz, 1 H), 5.90 (s, 2 H), 3.54 (q, J = 6.9 Hz, 2 H), 1.15 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1 (C), 144.5 (CH), 140.2 (C), 127.8 (CH), 127.8 (CH), 123.8 (C), 121.2 (CH), 121.1 (CH), 119.9 (C), 117.0 (C), 110.7 (CH), 71.1 (CH_2), 64.4 (CH_2), 15.0 (CH_3) ppm. MS (ESI): m/z = 261, 263 [M + H^+]. HRMS (CI): calcd. for $C_{14}H_{13}ClN_2O$ 261.0795; found 261.0794.

4-Chloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (6): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 9:1) to afford compound **6** (631 mg, 85% yield) as a white solid; m.p. 68–70 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3084, 2971, 2938, 2903, 1588, 1556, 1459, 1357, 1132, 1100, 1070, 1061, 813, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, J = 8.0 Hz, 1 H), 8.34 (d, J = 5.3 Hz, 1 H), 7.67 (d, J = 8.3 Hz, 1 H), 7.57 (td, J = 8.3, 7.1, 1.3 Hz, 1 H), 7.37 (td, J = 8.0, 1.1 Hz, 1 H), 7.19 (d, J = 5.3 Hz, 1 H), 5.87 (s, 2 H), 3.54 (q, J = 6.9 Hz, 2 H), 1.15 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.8 (C), 146.0 (C), 139.5 (C), 138.2 (C), 127.7 (CH), 123.4 (CH), 121.3 (CH), 120.0 (C), 116.9 (CH), 114.2 (CH), 110.4 (CH), 71.3 (CH_2), 64.5 (CH_2), 15.1 (CH_3) ppm. MS (CI): m/z = 261, 263 [M + H^+]. HRMS (CI): calcd. for $C_{14}H_{14}ClN_2O$ 261.0795; found 261.0795.

Phenyl-(9*H*-pyrido[2,3-*b*]indol-2-yl)amine (7):[19] A sealed pressure tube with stir bar was charged with 2-chloro-9*H*-pyrido[2,3-*b*]-indole (**1**; 100 mg, 0.498 mmol), [$Pd_2(dba)_3$] (37.0 mg, 0.04 mmol), and X-Phos (37.0 mg, 0.08 mmol). The tube was evacuated and back-filled with argon (repeated for three additional times). Aniline (60 μL, 0.65 mmol) and LiHMDS (1.0 M in THF, 1.5 mL, 3.00 mmol) were added and the reaction mixture was stirred at 65 °C overnight. After cooling to r.t., the solution was quenched with H_2O and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, then filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to afford compound **7** (80 mg, 62% yield) as a white solid. ^1H NMR (300 MHz, [D_6]acetone): δ = 10.56 (br. s, 1 H), 8.40 (br. s, 1 H), 8.20 (d, J = 8.5 Hz, 1 H), 7.91 (d, J = 7.7 Hz, 1 H), 7.85 (d, J = 7.7 Hz, 2 H), 7.48 (d, J = 8.1 Hz, 1 H), 7.31–7.25 (m, 3 H), 7.15 (t, J = 7.5 Hz, 1 H), 6.92 (t, J = 7.2 Hz, 1 H), 6.73 (d, J = 8.5 Hz, 1 H) ppm. MS (ESI): m/z = 258 [M + H^+].

General Procedure for C–N Bond Formation with 2- or 4-Chloro Derivatives: A sealed pressure tube with stir bar was charged with 2-chloro-9*H*-pyrido[2,3-*b*]indole (**1**) or 4-chloro-9*H*-pyrido[2,3-*b*]-indole (**3**) (100 mg, 0.498 mmol), [$Pd_2(dba)_3$] (37 mg, 0.04 mmol), X-Phos (38 mg, 0.08 mmol), and K_2CO_3 (190 mg, 1.37 mmol). The tube was evacuated and back-filled with argon (repeated for three additional times). Degassed *t*BuOH (1 mL) and the selected arylamine (1.3 equiv.) were added and the reaction mixture was stirred at 100 °C overnight. After cooling to r.t., the solution was quenched with H_2O and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, then filtered through Celite and the solvent was removed under reduced pressure.

(3-Nitrophenyl)-(9*H*-pyrido[2,3-*b*]indol-2-yl)amine (8): The crude product was purified by flash chromatography (CH_2Cl_2/petroleum ether, 9:1) to afford compound **8** (93 mg, 61% yield) as a red solid; m.p. >220 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3373, 3128, 1575, 1599, 1527, 1505, 1413, 1334, 1253, 1205, 1129, 800, 779, 756 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.62 (br. s, 1 H), 9.76 (br. s, 1 H), 8.93 (t, J = 2.3 Hz, 1 H), 8.31 (d, J = 8.3 Hz, 1 H), 8.15 (ddd, J = 8.2, 2.3, 0.8 Hz, 1 H), 7.95 (d, J = 7.5 Hz, 1 H), 7.73 (ddd, J = 8.2, 2.3, 0.8 Hz, 1 H), 7.56 (t, J = 8.2 Hz, 1 H), 7.43 (d, J = 7.8 Hz, 1 H), 7.30 (td, J = 7.5, 1.0 Hz, 1 H), 7.15 (td, J = 7.8, 1.0 Hz, 1 H), 6.74 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 153.3 (C), 150.4 (C), 148.3 (C), 143.1 (C), 137.7 (C), 130.4 (CH), 129.7 (CH), 124.2 (CH), 123.5 (CH), 121.3 (C), 119.3 (2 × CH), 114.2 (CH), 111.2 (CH), 111.0 (CH), 107.5 (C), 103.8 (CH) ppm. MS (CI, 100 °C): m/z = 305 [M + H^+]. HRMS (CI): calcd. for $C_{17}H_{13}N_4O_2$ 305.1039; found 305.1039.

(3-Methoxyphenyl)-(9*H*-pyrido[2,3-*b*]indol-2-yl)amine (9): The crude product was purified by flash chromatography (CH_2Cl_2/petroleum ether, 9:1) to afford compound **9** (100 mg, 70% yield) as a brown solid; m.p. 206–208 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3385, 3053, 1595, 1579, 1492, 1416, 1212, 1129, 1036, 776, 736 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.50 (br. s, 1 H), 9.20 (br. s, 1 H), 8.21 (d, J = 8.4 Hz, 1 H), 7.90 (d, J = 7.4 Hz, 1 H),7.70 (t, J = 2.3 Hz, 1 H), 7.38 (d, J = 7.9 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.25 (td, J = 8.4, 1.1 Hz, 1 H), 7.17 (t, J = 8.0 Hz, 1 H), 7.12 (td, J = 8.4, 1.1 Hz, 1 H), 6.68 (d, J = 8.4 Hz, 1 H), 6.48 (ddd, J = 8.0, 2.3, 0.8 Hz, 1 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 159.7 (C), 154.1 (C), 150.8 (C), 143.1 (C), 137.4 (C), 129.9 (CH), 129.2 (CH), 1237 (CH), 121.5 (C), 119.1

(CH), 119.0 (CH), 110.7 (CH), 110.4 (CH), 106.4 (C), 105.4 (CH), 103.8 (CH), 103.6 (CH), 54.8 (CH_3) ppm. MS (ESI): *m*/*z* = 290 [M + H^+]. HRMS (ESI): calcd. for $C_{18}H_{16}N_3O$ 290.1293; found 290.1291.

(2-Nitrophenyl)-(9*H*-pyrido[2,3-*b*]indol-2-yl)amine (10): The crude product was purified by flash chromatography (CH_2Cl_2/petroleum ether, 9:1) to afford compound **10** (80 mg, 53% yield) as a red solid; m.p. 204–206 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3390, 3297, 3057, 1569, 1595, 1458, 1496, 1414, 1318, 1254, 1202, 1133, 1077, 826, 733 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 10.38 (br. s, 1 H), 8.87 (d, *J* = 8.7 Hz, 1 H), 8.53 (br. s, 1 H), 8.25 (d, *J* = 8.5 Hz, 2 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 7.57 (td, *J* = 8.9, 1.5 Hz, 1 H), 7.42–7.37 (m, 3 H), 6.95 (td, *J* = 7.9, 1.1 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 151.7 (C), 150.4 (C), 137.9 (C), 137.4 (C), 136.8 (C), 134.8 (CH), 130.6 (CH), 125.6 (CH), 124.7 (CH), 121.7 (CH), 121.0 (C), 120.7 (CH), 119.7 (CH), 119.4 (CH), 111.0 (CH), 109.2 (C), 105.0 (CH) ppm. MS (CI, 150 °C): *m*/*z* = 305 [M + H^+]. HRMS (ESI): calcd. for $C_{17}H_{13}N_4O_2$ 305.1039; found 305.1038.

(3-Nitrophenyl)-(9*H*-pyrido[2,3-*b*]indol-4-yl)amine (13): The crude product was purified by flash chromatography (CH_2Cl_2/petroleum ether, 9:1) to afford compound **13** (110 mg, 79% yield) as a yellow solid; m.p. >220 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3411, 3058, 1594, 1574, 1504, 1334, 1259, 1065, 999, 880, 794 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.80 (br. s, 1 H), 9.10 (br. s, 1 H), 8.22 (d, *J* = 5.6 Hz, 1 H), 8.06 (t, *J* = 2.3 Hz, 1 H), 8.00 (d, *J* = 7.2 Hz, 1 H), 7.82 (ddd, *J* = 8.3, 2.3, 0.9 Hz, 1 H), 7.67 (ddd, *J* = 8.3, 2.3, 0.9 Hz, 1 H), 7.58 (t, *J* = 8.3 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.39 (td, *J* = 7.2, 1.1 Hz, 1 H), 7.15 (td, *J* = 8.0, 1.1 Hz, 1 H), 6.98 (d, *J* = 5.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 153.8 (C), 148.6 (C), 146.9 (CH), 144.2 (C), 143.4 (C), 137.9 (C), 130.4 (CH), 125.3 (CH), 124.9 (CH), 122.9 (CH), 119.6 (C), 118.9 (CH), 115.8 (CH), 113.1 (CH), 110.7 (CH), 104.9 (C), 103.4 (CH) ppm. MS (ESI): *m*/*z* = 305 [M + H^+]. HRMS (ESI): calcd. for $C_{17}H_{13}N_4O_2$ 305.1039; found 305.1041.

(3-Methoxyphenyl)-(9*H*-pyrido[2,3-*b*]indol-4-yl)amine (14): The crude product was purified by flash chromatography (CH_2Cl_2/EtOAc, 6:4) to afford compound **14** (100 mg, 70% yield) as a white solid; m.p. >220 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3440, 3051, 1615, 1594, 1577, 1490, 1455, 1341, 1262, 1158, 1042, 854, 762, 728 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.64 (br. s, 1 H), 8.50 (br. s, 1 H), 8.10 (d, *J* = 5.6 Hz, 1 H), 8.08 (d, *J* = 7.2 Hz, 1 H), 7.44 (d, *J* = 7.7 Hz, 1 H), 7.36 (td, *J* = 7.5, 0.9 Hz, 1 H), 7.25 (t, *J* = 8.4 Hz, 1 H), 7.14 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.89–6.86 (m, 2 H), 6.85 (d, *J* = 5.6 Hz, 1 H), 6.63 (dt, *J* = 8.4, 1.7 Hz, 1 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 160.1 (C), 153.7 (C), 146.8 (CH), 145.9 (C), 142.7 (C), 137.6 (C), 129.9 (CH), 124.9 (CH), 122.7 (CH), 120.0 (C), 118.8 (CH), 112.9 (CH), 110.5 (CH), 108.1 (CH), 106.4 (CH), 103.6 (C), 102.3 (CH), 54.9 (CH_3) ppm. MS (ESI): *m*/*z* = 290 [M + H^+]. HRMS (ESI): calcd. for $C_{18}H_{16}N_3O$ 290.1293; found 290.1288.

(2-Nitrophenyl)-(9*H*-pyrido[2,3-*b*]indol-4-yl)amine (15): The crude product was purified by flash chromatography (CH_2Cl_2/petroleum ether, 1:1) to afford compound **15** (121 mg, 80% yield) as a red solid; m.p. >220 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3330, 3037, 1615, 1588, 1498, 1458, 1347, 1256, 1153, 866, 776 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.93 (br. s, 1 H), 9.71 (br. s, 1 H), 8.31 (d, *J* = 5.5 Hz, 1 H), 8.24 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 7.61 (td, *J* = 7.9, 1.5 Hz, 1 H), 7.52 (d, *J* = 8.1 Hz, 1 H), 7.48–7.40 (m, 1 H), 7.43 (td, *J* = 8.1, 1.1 Hz, 1 H), 7.19–7.12 (m, 2 H), 7.11 (d, *J* = 5.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 153.6 (C), 147.0 (CH), 142.2 (C), 138.3 (C), 138.2 (C), 136.6 (C), 135.8 (CH), 126.3 (CH), 125.9 (CH), 121.8 (CH), 121.0 (CH), 119.9 (CH), 119.5 (CH), 119.2 (C), 111.1 (CH), 106.1 (C), 105.8 (CH) ppm. MS (ESI): *m*/*z* = 305 [M + H^+]. HRMS (ESI): calcd. for $C_{17}H_{13}N_4O_2$ 305.1039; found 305.1036.

General Procedure for C–N Bond Formation on 3-Chloro Derivatives: A sealed pressure tube with a stir bar was charged with 3-chloro-9*H*-pyrido[2,3-*b*]indole (**2**; 100 mg, 0.498 mmol), [Pd_2(dba)$_3$] (37 mg, 0.04 mmol), X-Phos (38 mg, 0.08 mmol), and NaO*t*Bu (132 mg, 1.37 mmol). The tube was evacuated and back-filled with argon (repeated for three additional times). Degassed *t*BuOH (1 mL) and aniline (1.3 equiv.) were added and the reaction mixture was stirred at 100 °C overnight. After cooling to r.t., the solution was quenched with H_2O and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried with $MgSO_4$, then filtered through Celite and the solvent was removed under reduced pressure.

Phenyl-(9*H*-pyrido[2,3-*b*]indol-3-yl)amine (11): The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 8:2) to afford compound **11** (100 mg, 78% yield) as a brown solid; m.p. >220 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3362, 3140, 1600, 1494, 1454, 1387, 1301, 1268, 1227, 783, 738 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.61 (br. s, 1 H), 8.29 (d, *J* = 2.3 Hz, 1 H), 8.24 (d, *J* = 2.3 Hz, 1 H), 8.13 (d, *J* = 7.7 Hz, 1 H), 8.01 (br. s, 1 H), 7.46 (d, *J* = 7.3 Hz, 1 H), 7.41 (td, *J* = 8.3, 8.1, 1.1 Hz, 1 H), 7.21–7.13 (m, 3 H), 6.93 (d, *J* = 7.7 Hz, 2 H), 6.72 (t, *J* = 7.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 148.1 (C), 146.1 (C), 141.1 (CH), 139.5 (C), 131.9 (C), 129.2 (2 × CH), 126.5 (CH), 121.4 (CH), 120.6 (CH), 120.2 (C), 118.9 (CH), 118.2 (CH), 115.2 (C), 114.1 (2 × CH), 111.1 (CH) ppm. MS (ESI): *m*/*z* = 260 [M + H^+]. HRMS (ESI): calcd. for $C_{17}H_{14}N_3$ 260.1188; found 260.1189.

(3-Methoxyphenyl)-(9*H*-pyrido[2,3-*b*]indol-3-yl)amine (12): The product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 8:2) to afford compound **12** (116 mg, 80% yield) as a yellow solid; m.p. 163–165 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3391, 3145, 3059, 1609, 1590, 1522, 1457, 1387, 1277, 1217, 1153, 1046, 750, 734 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.62 (br. s, 1 H), 8.31 (d, *J* = 2.3 Hz, 1 H), 8.24 (d, *J* = 2.3 Hz, 1 H), 8.14 (d, *J* = 7.7 Hz, 1 H), 8.01 (br. s, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H), 7.42 (td, *J* = 8.1, 0.8 Hz, 1 H), 7.16 (td, *J* = 7.9, 1.3 Hz, 1 H), 7.08 (t, *J* = 7.9 Hz, 1 H), 6.50 (dd, *J* = 8.1, 2.2 Hz, 1 H), 6.45 (t, *J* = 2.2 Hz, 1 H), 8.31 (dd, *J* = 8.1, 2.2 Hz, 1 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 160.4 (C), 148.3 (C), 147.6 (C), 141.4 (CH), 139.5 (C), 131.7 (C), 130.3 (CH), 126.5 (CH), 121.4 (CH), 121.1 (CH), 120.2 (C), 119.0 (CH), 115.2 (C), 111.2 (CH), 106.8 (CH), 103.7 (CH), 99.8 (CH), 54.7 (CH_3) ppm. MS (ESI): *m*/*z* = 290.2 [M + H^+]. HRMS (ESI): calcd. for $C_{18}H_{16}N_3O$: 290.1293; found 290.1293.

***N*,*N*′-Bis(3-methoxyphenyl)-9*H*-pyrido[2,3-*b*]indole-2,4-diamine (40):** A sealed pressure tube with a stir bar was charged with 2,4-dichloro-9*H*-pyrido[2,3-*b*]indole (**38**; 100 mg, 0.424 mmol), [Pd_2(dba)$_3$] (32 mg, 0.034 mmol), X-Phos (34 mg, 0.07 mmol), and K_2CO_3 (180 mg, 1.3 mmol). The tube was evacuated and back-filled with argon (repeated for three additional times). Degassed *t*BuOH (850 μL) and 3-methoxyaniline (148 μL, 1.1 mmol) were added and the reaction mixture was stirred at 100 °C overnight. After cooling to r.t., the solution was quenched with H_2O and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried with $MgSO_4$, then filtered through Celite and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/EtOAc, 9:1) to afford compound **40** (157 mg, 90% yield) as a white solid; m.p.

148–150 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3419, 3396, 1610, 1501, 1579, 1516, 1456, 1411, 1205, 1160, 807, 763, 736 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.44 (br. s, 1 H), 8.96 (br. s, 1 H), 8.28 (br. s, 1 H), 7.98 (d, J = 8.3 Hz, 1 H), 7.63 (t, J = 2.3 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 1 H), 7.28 (d, J = 8.3 Hz, 1 H), 7.24–7.19 (m, 2 H), 7.13 (t, J = 8.1 Hz, 1 H), 7.08 (t, J = 7.1 Hz, 1 H), 6.95–9.93 (m, 2 H), 6.63 (dd, J = 7.7, 1.9 Hz, 1 H), 6.46 (s, 1 H), 6.44 (dd, J = 8.9, 2.6 Hz, 1 H), 3.77 (s, 3 H), 3.76 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 160.0 (C), 159.7 (C), 155.1 (C), 152.6 (C), 147.2 (C), 143.5 (C), 143.0 (C), 136.6 (C), 129.8 (CH), 129.0 (CH), 122.6 (CH), 121.0 (C), 120.8 (CH), 118.7 (CH), 113.3 (CH), 110.4 (CH), 110.1 (CH), 107.8 (CH), 106.6 (CH), 105.1 (CH), 103.7 (CH), 97.4 (C), 88.6 (CH), 54.9 (CH$_3$), 54.8 (CH$_3$) ppm. MS (ESI): m/z = 411 [M + H$^+$]. HRMS (ESI): calcd. for $C_{25}H_{23}N_4O_2$ 411.1821; found 411.1821.

Phenyl(6-styryl-9*H*-pyrido[2,3-*b*]indol-2-yl)amine (36): A sealed pressure tube with a stir bar was charged with 2-chloro-6-styryl-9*H*-pyrido[2,3-*b*]indole[10] (54 mg, 0.178 mmol), [Pd$_2$(dba)$_3$] (13 mg, 0.014 mmol), X-Phos (13 mg, 0.029 mmol), and K_2CO_3 (74 mg, 0.53 mmol). The tube was evacuated and back-filled with argon (repeated for three additional times). Degassed *t*BuOH (1 mL) and aniline (1.3 equiv.) were added and the reaction mixture was stirred at 100 °C overnight. After cooling to r.t., the solution was quenched with H_2O and extracted with EtOAc (3 × 30 mL). The crude material was purified by flash chromatography (EtOAc/petroleum ether, 15:85) to afford compound **36** (40 mg, 62% yield) as a solid; m.p. >220 °C. IR (neat powder): $\tilde{\nu}$ = 3405, 3384, 3017, 2970, 1594, 1469, 1436, 1365, 1228, 1216, 1206, 961, 802, 748 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.59 (br. s, 1 H), 9.23 (br. s, 1 H), 8.24 (d, J = 8.5 Hz, 1 H), 8.15 (d, J = 0.8 Hz, 1 H), 7.84 (d, J = 7.5 Hz, 2 H), 7.60 (d, J = 7.3 Hz, 2 H), 7.55 (d, J = 8.3 Hz, 1 H), 7.40–7.18 (m, 8 H), 6.93–6.88 (m, 1 H), 6.71 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 154.4 (C), 151.4 (C), 141.8 (C), 137.6 (C), 137.3 (C), 130.1 (CH), 129.7 (CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.5 (C), 126.9 (CH), 126.0 (2 × CH), 125.3 (CH), 122.8 (CH), 122.0 (C), 120.3 (CH), 118.0 (2 × CH), 117.3 (CH), 110.9 (CH), 106.5 (C), 103.7 (CH) ppm. MS (ESI): m/z = 362 [M + H$^+$]. HRMS (ESI): calcd. for $C_{25}H_{20}N_3$ 362.1657; found 362.1653.

General Procedure for C–O Bond Formation: A solution of 2-chloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (**4**) or 4-chloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (**6**) (100 mg, 0.386 mmol), phenol (1.3 equiv.), [Pd$_2$(dba)$_3$] (28 mg, 0.03 mmol), X-Phos (26 mg, 0.06 mmol), and K_2CO_3 (160 mg, 1.15 mmol) in degassed toluene (1.5 mL/mmol) was stirred overnight at 110 °C in a sealed tube. After cooling to r.t., the products were extracted from the water layer with EtOAc, dried with $MgSO_4$, filtered through Celite and the solvents were removed under reduced pressure.

9-(Ethoxymethyl)-2-(3-nitrophenoxy)-9*H*-pyrido[2,3-*b*]indole (16): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 1:1) and recrystallization from EtOH to afford **16** (86 mg, 62% yield) as a yellow solid; m.p. 98–100 °C (EtOH). IR (neat powder): $\tilde{\nu}$ = 3118, 3101, 1596, 1574, 1523, 1467, 1424, 1345, 1313, 1274, 1221, 1071, 981, 822, 736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (d, J = 8.2 Hz, 1 H), 8.16–8.15 (m, 1 H), 8.08 (ddd, J = 5.8, 3.2, 2.1 Hz, 1 H), 8.00 (d, J = 7.5 Hz, 1 H), 7.62 (d, J = 8.2 Hz, 1 H), 7.58–7.55 (m, 2 H), 7.48 (td, J = 7.5, 1.1 Hz, 1 H), 7.32 (td, J = 8.2, 1.1 Hz, 1 H), 6.90 (d, J = 8.2 Hz, 1 H), 5.68 (s, 2 H), 3.41 (q, J = 6.9 Hz, 2 H), 1.06 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6 (C), 155.3 (C), 150.1 (C), 149.0 (C), 139.2 (C), 132.1 (CH), 130.0 (CH), 127.3 (CH), 126.2 (CH), 121.2 (CH), 121.0 (C), 120.2 (CH), 119.1 (CH), 116.3 (CH), 112.2 (C), 110.6 (CH), 104.0 (CH), 70.9 (CH$_2$), 64.4 (CH$_2$), 14.9 (CH$_3$) ppm. MS (SIMS): m/z = 363 [M]$^+$. HRMS (LSIMS): calcd. for $C_{20}H_{17}N_3O_4$ 363.1219; found 363.1218.

9-(Ethoxymethyl)-2-(3-methoxyphenoxy)-9*H*-pyrido[2,3-*b*]indole (17): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 7:3) to afford compound **17** (90 mg, 67% yield) as a brown oil. IR (NaCl): $\tilde{\nu}$ = 2959, 2918, 1592, 1574, 1421, 1340, 1212, 1137, 1042, 985, 778, 748, 735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.3 Hz, 1 H), 7.96 (d, J = 8.4 Hz, 1 H), 7.61 (d, J = 8.3 Hz, 1 H), 7.45 (td, J = 8.3, 7.4, 1.1 Hz, 1 H), 7.31 (td, J = 7.9, 1.1 Hz, 1 H), 7.28 (d, J = 7.5 Hz, 1 H), 6.81–6.74 (m, 4 H), 5.76 (s, 2 H), 3.81 (s, 3 H), 3.47 (q, J = 7.0 Hz, 2 H), 1.09 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0 (C), 160.9 (C), 156.0 (C), 150.6 (C), 139.1 (C), 131.7 (CH), 129.9 (CH), 125.8 (CH), 121.3 (C), 121.0 (CH), 120.0 (CH), 113.3 (CH), 111.4 (C), 110.5 (CH), 110.2 (CH), 107.0 (CH), 103.5 (CH), 70.9 (CH$_2$), 64.4 (CH$_2$), 55.5 (CH$_3$), 14.9 (CH$_3$) ppm. MS (CI): m/z = 349 [M + H$^+$]. HRMS (CI): calcd. for $C_{21}H_{21}N_2O_3$ 349.1552; found 349.1554.

9-(Ethoxymethyl)-4-(3-nitrophenoxy)-9*H*-pyrido[2,3-*b*]indole (18): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 9:1) to afford compound **18** (120 mg, 86% yield) as a brown solid; m.p. 85–90 °C (EtOH). IR (neat powder): $\tilde{\nu}$ = 3047, 2977, 2882, 1601, 1568, 1524, 1460, 1347, 1258, 1080, 801, 790 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (d, J = 5.6 Hz, 1 H), 8.15–8.11 (m, 1 H), 8.13 (d, J = 7.9 Hz, 1 H), 8.08 (t, J = 2.1 Hz, 1 H), 7.68 (dd, J = 8.3, 8.1 Hz, 1 H), 7.67 (d, J = 7.9 Hz, 1 H), 7.58–7.55 (m, 1 H), 7.55 (td, J = 8.2, 1.1 Hz, 1 H), 7.31 (td, J = 8.2, 1.1 Hz, 1 H), 6.59 (d, J = 5.6 Hz, 1 H), 5.97 (s, 2 H), 3.59 (q, J = 6.9 Hz, 2 H), 1.17 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7 (C), 155.6 (C), 154.4 (C), 149.5 (C), 147.4 (CH), 139.0 (C), 130.9 (CH), 127.0 (CH), 126.2 (CH), 123.4 (CH), 121.4 (CH), 119.8 (CH), 119.4 (C), 115.4 (CH), 110.4 (CH), 106.7 (C), 104.0 (CH), 71.4 (CH$_2$), 64.5 (CH$_2$), 15.1 (CH$_3$) ppm. MS (SIMS): m/z = 363 [M$^+$]. HRMS (LSIMS): calcd. for $C_{20}H_{17}N_3O_4$ 363.1219; found 363.1219.

9-(Ethoxymethyl)-4-(3-methoxyphenoxy)-9*H*-pyrido[2,3-*b*]indole (19): The product was purified by column chromatography on silica gel (CH_2Cl_2) to afford compound **19** (105 mg, 78% yield) as a yellow oil. IR (NaCl): $\tilde{\nu}$ = 3053, 1590, 1565, 1483, 1459, 1262, 1170, 1137, 1081, 751 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, J = 5.8 Hz, 1 H), 8.26 (d, J = 7.7 Hz, 1 H), 7.66 (d, J = 8.1 Hz, 1 H), 7.52 (td, J = 8.3, 7.3, 1.4 Hz, 1 H), 7.36 (d, J = 8.3 Hz, 1 H), 7.32 (td, J = 7.7, 1.4 Hz, 1 H), 6.85–6.79 (m, 3 H), 6.55 (d, J = 5.8 Hz, 1 H), 5.95 (s, 2 H), 3.83 (s, 3 H), 3.58 (q, J = 6.9 Hz, 2 H), 1.16 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2 (C), 160.3 (C), 155.6 (C), 154.3 (C), 147.4 (CH), 138.7 (C), 130.6 (CH), 126.4 (CH), 123.5 (CH), 121.1 (CH), 119.9 (C), 112.8 (CH), 111.1 (CH), 110.0 (CH), 106.7 (CH), 106.0 (C), 103.4 (CH), 71.3 (CH$_2$), 64.3 (CH$_2$), 55.5 (CH$_3$), 15.1 (CH$_3$) ppm. MS (CI): m/z = 349 [M + H$^+$]. HRMS (CI): calcd. for $C_{21}H_{21}N_2O_3$ 349.1552; found 349.1553.

9-(Ethoxymethyl)-2,4-bis(3-methoxyphenoxy)-9*H*-pyrido[2,3-*b*]-indole (41): A solution of 2,4-dichloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (**39**; 50 mg, 0.17 mmol), 3-methoxyphenol (41 μL, 0.391 mmol), [Pd$_2$(dba)$_3$] (12 mg, 0.013 mmol), X-Phos (13 mg, 0.032 mmol), and K_2CO_3 (71 mg, 0.51 mmol) in degassed toluene (390 μL) was stirred overnight at 110 °C in a sealed tube. After cooling to r.t., the products were extracted from the water layer with EtOAc, dried with $MgSO_4$, filtered through Celite and the solvents were removed under reduced pressure. The product was purified by column chromatography on silica gel (CH_2Cl_2/petro-

leum ether, 1:1) to afford compound **41** (64 mg, 80% yield) as a brown solid; m.p. 96–98 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3070, 2974, 2939, 2839, 1588, 1568, 1463, 1342, 1190, 1152, 1034, 1024, 834, 755 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 8.01 (d, J = 7.5 Hz, 1 H), 7.68 (d, J = 8.3 Hz, 1 H), 7.44 (td, J = 8.1, 1.0 Hz, 1 H), 7.42 (t, J = 8.1 Hz, 1 H), 7.30 (t, J = 8.9 Hz, 2 H), 6.96 (t, J = 2.2 Hz, 1 H), 6.91 (t, J = 8.1 Hz, 2 H), 6.80–6.73 (m, 2 H), 6.76 (s, 1 H), 6.04 (s, 1 H), 5.66 (s, 2 H), 3.78 (s, 3 H), 3.73 (s, 3 H), 3.38 (q, J = 7.0 Hz, 2 H), 0.98 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]acetone): δ = 163.9 (C), 163.6 (C), 162.3 (C), 161.7 (C), 156.6 (C), 156.2 (C), 152.8 (C), 139.1 (C), 131.6 (CH), 130.5 (CH), 126.0 (CH), 122.8 (CH), 121.9 (CH), 120.9 (C), 113.7 (CH), 113.5 (CH), 112.3 (CH), 111.0 (CH), 110.9 (CH), 107.6 (CH), 107.5 (CH), 102.1 (C), 91.3 (CH), 71.4 (CH_2), 64.8 (CH_2), 55.9 (CH_3), 55.7 (CH_3), 15.1 (CH_3) ppm. MS (CI, 200 °C): m/z = 471 [M + H^+]. HRMS (CI): calcd. for $C_{28}H_{27}N_2O_5$ 471.1920; found 471.1920.

General Procedure for the Sonogashira Reaction on Compound 1: A Schlenk tube with a stir bar was charged with [$PdCl_2(CH_3CN)_2$] (11 mg, 0.04 mmol), X-Phos (39 mg, 0.08 mmol), 2-chloro-9*H*-pyrido[2,3-*b*]indole (**1**; 100 mg, 0.499 mmol), and Cs_2CO_3 (424 mg, 1.3 mmol). The tube was evacuated and back-filled with argon (repeated for three additional times). Acetonitrile (900 μL, 0.6 mmol/mL) was added (when degassed solvent was used) and then the alkyne (1.3 equiv.) was injected. The reaction mixture was stirred overnight at 70 °C, then, after cooling to r.t., the resulting mixture was then quenched with H_2O and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered through Celite and the solvents were removed under reduced pressure.

2-(Phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (20): The product was purified by column chromatography on silica gel (CH_2Cl_2) to afford compound **20** (85 mg, 64% yield) as a yellow solid; m.p. >220 °C. IR (neat powder): $\tilde{\nu}$ = 3144, 3084, 3054, 2202, 1599, 1490, 1460, 1411, 1283, 997, 826 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.87 (br. s, 1 H), 8.54 (d, J = 7.9 Hz, 1 H), 8.19 (d, J = 7.7 Hz, 1 H), 7.66–7.62 (m, 2 H), 7.53 (d, J = 7.1 Hz, 1 H), 7.50–7.47 (m, 4 H), 7.48 (ddd, J = 8.1, 7.1, 1.1 Hz, 1 H), 7.25 (ddd, J = 8.1, 7.1, 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 151.6 (C), 139.6 (C), 137.8 (C), 131.6 (2×CH), 129.2 (CH), 128.8 (2×CH), 128.6 (CH), 127.3 (C), 121.7 (CH), 121.5 (CH), 120.1 (C), 119.8 (CH), 118.9 (CH), 115.2 (C), 111.4 (CH), 90.3 (C), 87.8 (C) ppm. MS (EI): m/z = 268 $[M]^+$. HRMS (CI): calcd. for $C_{14}H_{13}N_2$ 268.1000; found 268.1002.

2-(Pent-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (21): The product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1) to afford compound **21** (71 mg, 61% yield) as a yellow solid; m.p. 158–160 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3156, 3056, 2951, 2926, 2854, 2223, 1602, 1575, 1457, 1413, 1229, 1119, 998, 816, 784, 733 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 11.75 (br. s, 1 H), 8.45 (d, J = 7.8 Hz, 1 H), 8.14 (d, J = 7.6 Hz, 1 H), 7.50 (d, J = 7.6 Hz, 1 H), 7.45 (td, J = 8.1, 6.8, 1.1 Hz, 1 H), 7.27 (d, J = 7.8 Hz, 1 H), 7.22 (ddd, J = 8.1, 6.8, 1.7 Hz, 1 H), 2.51–2.44 (m, 2 H), 1.61 (q, J = 7.0 Hz, 2 H), 1.04 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 151.6 (C), 139.4 (C), 138.7 (C), 128.5 (CH), 126.9 (CH), 121.3 (CH), 120.1 (C), 119.6 (CH), 118.3 (CH), 114.5 (C), 111.3 (CH), 89.6 (C), 81.9 (C), 21.5 (CH_2), 20.5 (CH_2), 13.3 (CH_3) ppm. MS (EI): m/z = 234 $[M]^+$.

Procedure for the Sonogashira Reaction on Compounds 4–6: A Schlenk tube with stir bar was charged with [$PdCl_2(CH_3CN)_2$] (0.08 equiv.), X-Phos (0.16 equiv.), chloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (**4**–**6**) (1 equiv.), and Cs_2CO_3 (2.6 equiv.). The tube was evacuated and back-filled with argon (repeated for three additional times). Acetonitrile (0.6 mmol/mL) was added (when degassed solvent was used), the alkyne (1.3 equiv.) was injected and the reaction mixture was stirred at 70 °C or 90 °C (see Table 3) overnight. After cooling to r.t., the resulting mixture was then quenched with H_2O and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered through Celite and the solvents were removed under reduced pressure.

9-(Ethoxymethyl)-2-(phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (22): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 7:3) to afford compound **22** (101 mg, 80% yield) as a yellow solid; m.p. 88–90 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3052, 2211, 1587, 1565, 1469, 1422, 139, 1345, 1122, 1075, 1055, 1008, 784, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, J = 7.9 Hz, 1 H), 8.05 (d, J = 7.5 Hz, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 7.67–7.64 (m, 2 H), 7.54 (td, J = 8.2, 7.5, 1.1 Hz, 1 H), 7.49 (d, J = 7.9 Hz, 1 H), 7.39–7.37 (m, 3 H), 7.33 (td, J = 7.1, 1.0 Hz, 1 H), 5.97 (s, 2 H), 3.57 (q, J = 6.9 Hz, 2 H), 1.16 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.8 (C), 140.1 (C), 139.0 (C), 132.1 (2×CH), 128.9 (CH), 128.5 (2×CH), 128.2 (CH), 127.5 (CH), 122.7 (C), 121.1 (2×CH), 120.7 (C), 120.3 (CH), 115.8 (C), 110.8 (CH), 90.1 (C), 89.1 (C), 71.1 (CH_2), 64.3 (CH_2), 15.1 (CH_3) ppm. MS (CI): m/z = 283 [M + H^+].

9-(Ethoxymethyl)-2-(pent-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (23): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 6:4) to afford compound **23** (96 mg, 85% yield) as a yellow solid; m.p. 73–75 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3010, 2968, 2930, 2870, 2219, 1584, 1565, 1463, 1421, 1388, 1340, 1230, 1055, 784, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, J = 7.9 Hz, 1 H), 8.02 (d, J = 7.6 Hz, 1 H), 7.65 (d, J = 8.2 Hz, 1 H), 7.51 (td, J = 8.2, 7.6, 1.3 Hz, 1 H), 7.33 (d, J = 7.9 Hz, 1 H), 7.31 (td, J = 8.3, 1.0 Hz, 1 H), 5.94 (s, 2 H), 3.53 (q, J = 7.0 Hz, 2 H), 2.48 (t, J = 7.3 Hz, 2 H), 1.71 (sext, J = 7.3 Hz, 2 H), 1.13 (t, J = 7.0 Hz, 3 H), 1.09 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.7 (C), 139.9 (C), 139.7 (C), 128.1 (CH), 127.2 (CH), 120.9 (CH), 120.9 (CH), 120.7 (C), 119.9 (CH), 115.2 (C), 110.7 (CH), 90.6 (C), 81.7 (C), 71.0 (CH_2), 64.1 (CH_2), 22.0 (CH_2), 21.6 (CH_2), 15.0 (CH_3), 13.7 (CH_3) ppm. MS (ESI): m/z = 247 [M + H^+ – EtOH$^+$], 293 [M + H^+].

2-(Cyclohexyleth-1-ynyl)-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (24): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 4:6) to afford compound **24** (111 mg, 87% yield) as a brown oil. IR (NaCl): $\tilde{\nu}$ = 2048, 2927, 2852, 1564, 1587, 1468, 1419, 1385, 1338, 1217, 1095, 1078, 1052, 787, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, J = 7.9 Hz, 1 H), 8.01 (d, J = 7.9 Hz, 1 H), 7.64 (d, J = 8.3 Hz, 1 H), 7.51 (td, J = 8.3, 7.2, 1.3 Hz, 1 H), 7.33 (d, J = 7.9 Hz, 1 H), 7.31 (td, J = 7.9, 0.8 Hz, 1 H), 5.93 (s, 2 H), 3.53 (q, J = 7.0 Hz, 2 H), 2.68 (m, 1 H), 1.97 (br. s, 2 H), 1.80 (br. s, 2 H), 1.62 (br. s, 3 H), 1.40 (br. s, 3 H), 1.13 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.7 (C), 140.0 (C), 139.9 (C), 128.1 (CH), 127.2 (CH), 120.9 (CH), 120.9 (CH), 120.8 (C), 120.1 (CH), 115.2 (C), 110.7 (CH), 94.7 (C), 81.5 (C), 71.1 (CH_2), 64.2 (CH_2), 32.2 (2×CH_2), 29.9 (CH), 26.0 (CH_2), 25.1 (2×CH_2), 13.7 (CH_3) ppm. MS (ESI): m/z = 333 [M + H^+]. HRMS (CI): calcd. for $C_{22}H_{25}N_2O$ 333.1967; found 333.1967.

9-(Ethoxymethyl)-3-(phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (25): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 8:2) to afford compound **25** (120 mg, 95% yield) as a yellow solid; m.p. 68–70 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3029, 2211, 1738, 1592, 1493, 1461,

1374, 1229, 1068, 1057, 895, 782, 750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (d, J = 1.9 Hz, 1 H), 8.45 (d, J = 1.9 Hz, 1 H), 8.06 (d, J = 7.7 Hz, 1 H), 7.66 (d, J = 8.3 Hz, 1 H), 7.60–7.53 (m, 3 H), 7.41–7.32 (m, 4 H), 5.93 (s, 2 H), 3.57 (q, J = 6.9 Hz, 2 H), 1.16 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.8 (C), 149.2 (CH), 139.9 (C), 131.6 (2 × CH), 130.9 (CH), 128.5 (2 × CH), 128.3 (CH), 127.6 (CH), 123.3 (C), 121.3 (CH), 121.1 (CH), 120.5 (C), 115.7 (C), 112.2 (C), 110.7 (CH), 90.4 (C), 87.6 (C), 71.1 (CH_2), 64.4 (CH_2), 15.0 (CH_3) ppm. MS (ESI): m/z = 281 [M + H$^+$ – EtOH$^+$], 327 [M + H$^+$].

9-(Ethoxymethyl)-3-(pent-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (26): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 8:2) to afford compound **26** (91 mg, 81% yield) as a yellow solid; m.p. 58–60 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3056, 2967, 2930, 2100, 1596, 1476, 1463, 1388, 1372, 1238, 1061, 1005, 902, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 1.9 Hz, 1 H), 8.32 (d, J = 1.9 Hz, 1 H), 8.02 (d, J = 7.7 Hz, 1 H), 7.64 (d, J = 8.3 Hz, 1 H), 7.53 (td, J = 8.1, 7.1, 1.1 Hz, 1 H), 7.32 (td, J = 7.7, 7.1, 1.0 Hz, 1 H), 5.77 (s, 1 H), 3.43 (q, J = 7.0 Hz, 2 H), 2.35 (t, J = 7.0 Hz, 2 H), 1.58 (q, J = 7.0 Hz, 2 H), 1.03 (t, J = 7.0 Hz, 3 H), 0.99 (t, J = 7.0 Hz, 3 H), 1.09 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5 (C), 149.2 (CH), 139.8 (C), 130.9 (CH), 127.4 (CH), 121.0 (2 CH), 120.5 (C), 115.6 (C), 113.0 (C), 110.6 (CH), 91.1 (C), 78.6 (C), 71.1 (CH_2), 64.3 (CH_2), 22.3 (CH_2), 21.6 (CH_2), 15.0 (CH_3), 13.7 (CH_3) ppm. MS (CI): m/z = 293 [M + H$^+$]. HRMS (CI): calcd. for $C_{19}H_{21}N_2O$ 293.1654; found 293.1654.

3-(Cyclohexyleth-1-ynyl)-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (27): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 7:3) to afford compound **27** (81 mg, 63% yield) as a brown oil. IR (NaCl): $\tilde{\nu}$ = 3048, 2926, 2852, 1596, 1480, 1448, 1231, 1094, 1073, 752, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, J = 1.9 Hz, 1 H), 8.32 (d, J = 1.9 Hz, 1 H), 8.02 (d, J = 7.5 Hz, 1 H), 7.64 (d, J = 8.2 Hz, 1 H), 7.53 (td, J = 8.2, 7.5, 1.0 Hz, 1 H), 7.32 (td, J = 7.5, 1.0 Hz, 1 H), 5.90 (s, 2 H), 3.53 (q, J = 6.9 Hz, 2 H), 2.65 (m, 1 H), 1.89 (br. s, 2 H), 1.79 (br. s, 2 H), 1.39 (br. s, 4 H), 1.27 (br. s, 2 H), 1.13 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.6 (C), 149.2 (CH), 139.9 (C), 131.0 (CH), 127.4 (CH), 121.1 (2 × CH), 120.6 (C), 115.6 (C), 113.1 (C), 110.6 (CH), 95.3 (C), 78.4 (C), 71.1 (CH_2), 64.3 (CH_2), 32.9 (3 × CH_2), 29.9 (CH), 26.0 (CH_2), 25.0 (CH_2), 15.0 (CH_3) ppm. MS (CI): m/z = 333 [M + H$^+$]. HRMS (CI): calcd. for $C_{22}H_{25}N_2O$: 333.1966; found 333.1966.

9-(Ethoxymethyl)-4-(phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (28): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 9:1) to afford compound **28** (136 mg, 95% yield) as a yellow solid; m.p. 89–91 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3052, 2212, 1738, 1581, 1482, 1558, 1460, 1374, 1211, 1078, 819, 749, 733 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, J = 7.7 Hz, 1 H), 8.45 (d, J = 5.2 Hz, 1 H), 7.72 (dd, J = 7.5, 3.8 Hz, 2 H), 7.68 (d, J = 8.1 Hz, 1 H), 7.57 (td, J = 8.2, 7.1, 1.0 Hz, 1 H), 7.48–7.43 (m, 3 H), 7.37 (td, J = 8.1, 1.0 Hz, 1 H), 7.30 (d, J = 5.2 Hz, 1 H), 5.95 (s, 2 H), 3.52 (q, J = 6.9 Hz, 2 H), 1.16 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.0 (C), 145.4 (CH), 139.7 (C), 132.0 (2 × CH), 129.3 (CH), 128.7 (2 × CH), 127.5 (CH), 124.3 (C), 122.7 (CH), 122.6 (C), 121.0, (CH), 120.9 (C), 118.6 (CH), 115.8 (C), 110.3 (CH), 97.3 (C), 86.6 (C), 71.1 (CH_2), 64.4 (CH_2), 15.1 (CH_3) ppm. MS (ESI): m/z = 281.3 [M + H$^+$ – EtOH$^+$], 327.0 [M + H$^+$].

9-(Ethoxymethyl)-4-(pent-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (29): The product was purified by column chromatography on silica gel (CH_2Cl_2) to afford compound **29** (101 mg, 90% yield) as a yellow solid; m.p. 72–74 °C (EtOH). IR (NaCl): $\tilde{\nu}$ = 3057, 2966, 2928, 2223, 1582, 1560, 1462, 1413, 1287, 1078, 1063, 814, 739 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 7.5 Hz, 1 H), 8.38 (d, J = 5.2 Hz, 1 H), 7.65 (d, J = 8.3 Hz, 1 H), 7.54 (td, J = 8.3, 7.5, 1.1 Hz, 1 H), 7.33 (td, J = 8.3, 1.1 Hz, 1 H), 7.17 (d, J = 5.2 Hz, 1 H), 5.92 (s, 2 H), 3.54 (q, J = 7.0 Hz, 2 H), 2.63 (t, J = 7.3 Hz, 2 H), 1.81 (m, J = 7.3 Hz, 2 H), 1.16 (t, J = 7.3 Hz, 3 H), 1.14 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0 (CH), 139.5 (C), 127.4 (CH), 125.7 (C), 122.5 (CH), 121.1 (2 C), 120.9 (CH), 118.9 (CH), 116.1 (C), 110.3 (CH), 99.8 (C), 78.3 (C), 71.1 (CH_2), 64.4 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 15.1 (CH_3), 13.8 (CH_3) ppm. MS (CI): m/z = 293 [M + H$^+$]. HRMS (CI): calcd. for $C_{19}H_{21}N_2O$ 293.1654; found 293.1654.

4-(Cyclohexyleth-1-ynyl)-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (30): The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 7:3) to afford compound **30** (102 mg, 80% yield) as a brown oil. IR (NaCl): $\tilde{\nu}$ = 2927, 2852, 2221, 1583, 1560, 1485, 1461, 1360, 1285, 1083, 819, 792 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, J = 7.9 Hz, 1 H), 8.38 (d, J = 5.2 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.53 (t, J = 7.7 Hz, 1 H), 7.34 (t, J = 7.7 Hz, 1 H), 7.17 (d, J = 5.2 Hz, 1 H), 5.92 (s, 2 H), 3.54 (q, J = 7.0 Hz, 2 H), 2.82 (m, 1 H), 2.06 (br. s, 2 H), 1.84 (br. s, 2 H), 1.69 (br. s, 3 H), 1.45 (br. s, 3 H), 1.14 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.0 (C), 145.3 (CH), 139.4 (C), 127.2 (CH), 125.5 (C), 122.4 (CH), 121.0 (C), 120.7 (CH), 118.9 (CH), 115.8 (C), 110.1 (CH), 103.5 (C), 78.0 (C), 71.0 (CH_2), 64.2 (CH_2), 32.6 (2 × CH_2), 30.3 (CH), 25.9 (CH_2), 25.1 (2 × CH_2), 15.0 (CH_3) ppm. MS (CI): m/z = 333 [M + H$^+$]. HRMS (CI): calcd. for $C_{22}H_{25}N_2O$ 333.1966; found 333.1968.

3-Chloro-6-(2-phenyleth-1-ynyl)-9-(phenylsulfonyl)-9*H*-pyrido[2,3-*b*]-indole (32): To a solution of 6-bromo-3-chloro-9-(phenylsulfonyl)-9*H*-pyrido[2,3-*b*]indole (**31**)[10] (100 mg, 0.24 mmol, 1 equiv.) in anhydrous DMF (1.5 mL) under argon, $[Pd(Cl)_2(PPh_3)_2]$ (17 mg, 0.024 mmol, 0.1 equiv.), CuI (9 mg, 0.048 mmol, 0.2 equiv.), PPh_3 (6 mg, 0.024 mmol, 0.1 equiv.), 1-ethynylbenzene (0.079 mL, 0.72 mmol, 3 equiv.), and Et_3N (3 mL) were added. The mixture was stirred at 80 °C overnight and then poured into water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) and concentrated under reduced pressure. The crude residue was purified over silica gel column (CH_2Cl_2/petroleum ether, 1:1) to afford the product **32** (98 mg, 92% yield) as a white solid; m.p. 190–194 °C. IR (neat powder): $\tilde{\nu}$ = 3135, 3061, 1494, 1468, 1434, 1380, 1360, 1264, 1211, 1183, 1090, 973, 830, 727, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, J = 2.3 Hz, 1 H), 8.46 (d, J = 8.9 Hz, 1 H), 8.15 (d, J = 2.3 Hz, 2 H), 8.10 (m, 2 H), 7.76 (dd, J = 8.9, 1.7 Hz, 1 H), 7.58–7.54 (m, 3 H), 7.47–7.36 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2 (C), 146.1 (CH), 138.4 (C), 137.9 (C), 134.4 (CH), 132.6 (CH), 131.8 (2 × CH), 129.2 (2 × CH), 128.6 (CH), 128.6 (2 × CH), 128.3 (CH), 127.8 (C), 127.7 (2 × CH), 124.2 (CH), 123.1 (C), 122.0 (C), 119.5 (C), 119.3 (C), 115.4 (CH), 90.0 (C), 88.7 (C) ppm. MS (ESI): m/z = 443, 445 [M + H$^+$].

3-Chloro-6-(2-phenylethyl)-9-(phenylsulfonyl)-9*H*-pyrido[2,3-*b*]-indole (33): A solution of 3-chloro-6-(2-phenylethynyl)-9-(phenylsulfonyl)-9*H*-pyrido[2,3-*b*]indole (**32**; 200 mg, 0.45 mmol, 1 equiv.) in anhydrous ethanol (25 mL) was treated with 10% Pd/C (50 mg, 0.047 mmol, 0.1 equiv.) and then stirred at r.t. under an atmosphere of H_2 overnight. The reaction mixture was filtered through Celite and then concentrated under reduced pressure. The crude product (pale-yellow solid) was purified over silica gel chromatography (CH_2Cl_2/petroleum ether, 7:3) to afford compound **33** (183 mg, 91% yield) as a white solid; m.p. 158–162 °C. IR (neat powder): $\tilde{\nu}$

= 3057, 3023, 2926, 1494, 1475, 1432, 1376, 1366, 1255, 1182, 1712, 1090, 977, 908, 713, 683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, J = 2.3 Hz, 1 H), 8.36 (d, J = 8.7 Hz, 1 H), 8.12 (m, 3 H), 7.67 (s, 1 H), 7.56–7.52 (m, 1 H), 7.45–7.38 (m, 3 H), 7.32–7.18 (m, 5 H), 3.12–2.97 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2 (C), 145.4 (CH), 141.4 (C), 138.7 (C), 138.1 (C), 137.0 (C), 134.2 (CH), 130.0 (CH), 129.1 (2×CH), 128.6 (2×CH), 128.6 (2×CH), 128.9 (2×CH), 127.6 (CH), 127.5 (C), 126.3 (CH), 122.0 (C), 120.6 (CH), 120.0 (C), 115.1 (CH), 38.2 (CH_2), 38.8 (CH_2) ppm. MS (ESI): m/z = 447.1 [M + H^+].

3-Chloro-6-(2-phenylethyl)-9*H*-pyrido[2,3-*b*]indole (34): To a solution of 3-chloro-6-(2-phenylethyl)-9-(phenylsulfonyl)-9*H*-pyrido[2,3-*b*]indole (**33**; 170 mg, 0.38 mmol, 1 equiv.) in THF (18 mL) under argon, TBAF (1 M in THF, 1.91 mL, 1.91 mmol, 5 equiv.) was added dropwise. The reaction was heated to reflux for 4 h and then evaporated. The crude product was purified by silica gel chromatography (EtOAc/petroleum ether, 1:1) to afford compound **34** (108 mg, 91% yield) as a white solid; m.p. 216–220 °C. IR (neat powder): $\tilde{\nu}$ = 3111, 3028, 2921, 2851, 1600, 1490, 1453, 1389, 1271, 1236, 1087, 1030, 931, 732, 682 cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 11.88 (br. s, 1 H), 8.60 (d, J = 2.5 Hz, 1 H), 8.39 (d, J = 2.4 Hz, 1 H), 8.06 (s, 1 H), 7.43–7.35 (m, 3 H), 7.25 (m, 3 H), 7.18 (m, 1 H), 3.06–2.92 (m, 4 H) ppm. ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 150.3 (C), 143.8 (CH), 141.6 (C), 138.2 (C), 133.0 (C), 128.4 (2×CH), 128.3 (CH), 128.2 (2×CH), 127.8 (CH), 125.8 (CH), 121.5 (C), 120.9 (CH), 119.6 (C), 116.3 (C), 111.2 (CH), 37.7 (CH_2), 37.3 (CH_2) ppm. MS (ESI): m/z = 307.2 [M + H^+].

***N*-(3-Methoxyphenyl)-6-(2-phenylethyl)-9*H*-pyrido[2,3-*b*]indol-3-amine (35):** 3-Chloro-6-(2-phenylethyl)-9*H*-pyrido[2,3-*b*]indole (**34**; 50 mg, 0.16 mmol, 1 equiv.), [$Pd_2(dba)_3$] (8.2 mg, 0.008 mmol, 0.05 equiv.), X-Phos (8.1 mg, 0.016 mmol, 0.1 equiv.), and NaO*t*Bu (36 mg, 0.37 mmol, 2.2 equiv.) were introduced into a Schlenk tube and flushed with N_2. *t*BuOH (0.255 mL) and *m*-anisidine (25 mg, 0.20 mmol, 1.2 equiv.) were then added and the reaction was heated to 100 °C overnight. After cooling, the mixture was filtered through Celite and evaporated under reduced pressure. The crude product (yellow oil) was purified by silica gel chromatography (EtOAc/petroleum ether, 4:6 to 6:4) to afford compound **35** (18 mg, 29% yield) as a green solid; m.p. 161–165 °C. IR (neat powder): $\tilde{\nu}$ = 3359, 3145, 3022, 1595, 1494, 1467, 1383, 1218, 1151, 1038, 968, 891, 809, 771, 685 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.94 (br. s, 1 H), 8.36 (br. s, 1 H), 8.18 (s, 1 H), 7.78 (s, 1 H), 7.41 (d, J = 8.3 Hz, 1 H), 7.32–7.14 (m, 7 H), 6.52 (d, J = 8.1 Hz, 1 H), 6.47–6.44 (m, 2 H), 3.77 (s, 3 H), 3.12–2.97 (m, 4 H) ppm. MS (ESI): m/z = 394.3 [M + H^+].

4-Chloro-9*H*-pyrido[2,3-*b*]indole *N*-Oxide (37): *m*-Chloroperbenzoic acid 70% (1.50 g, 8.6 mmol) was added to a 0.06 M stirred solution of 4-chloro-9*H*-pyrido[2,3-*b*]indole (**3**; 1.05 g, 5.2 mmol) at r.t. in $CHCl_3$. The reaction mixture was stirred for 12 h at r.t., then the solution was neutralized with saturated aqueous solution of K_2CO_3 and the layers were separated. The organic layer was washed with brine and dried with $MgSO_4$, filtered, and concentrated in vacuo. Trituration of the crude residue from Et_2O then filtration afforded compound **37** (786 mg, 64% yield) as a brown solid; m.p. >220 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3052, 2980, 1602, 1571, 1469, 1458, 1434, 1292, 1195, 1085, 932 cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 12.93 (br. s, 1 H), 8.38 (d, J = 7.9 Hz, 1 H), 8.36 (d, J = 6.8 Hz, 1 H), 7.62–7.60 (m, 2 H), 7.38 (ddd, J = 8.1, 5.1, 2.8 Hz, 1 H), 7.33 (d, J = 6.8 Hz, 1 H) ppm. MS (CI): m/z = 186 [M + H^+].

2,4-Dichloro-9*H*-pyrido[2,3-*b*]indole (38): Methanesulfonyl chloride (2 equiv.) was added to a 0.4 M stirred suspension of 4-chloro-9*H*-pyrido[2,3-*b*]indole *N*-oxide (**37**) (1 equiv.) in DMF. The reaction mixture was heated at 100 °C for 12 h, then cooled to r.t. and the resulting mixture was cautiously quenched at 0 °C with H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered and the solvents were removed under reduced pressure. Trituration of the crude residue from MeOH then filtration afforded compound **38** (600 mg, 74% yield) as a white solid; m.p. >220 °C (MeOH). IR (neat powder): $\tilde{\nu}$ = 3139, 3062, 1598, 1560, 1452, 1401, 1314, 1201, 1118, 868, 728 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 12.43 (br. s, 1 H), 8.35 (d, J = 7.9 Hz, 1 H), 7.58–7.56 (m, 2 H), 7.48 (s, 1 H), 7.34 (td, J = 8.1, 2.5 Hz, 1 H) ppm. MS (CI): m/z = 237 [M + H^+] at 200 °C. HRMS (CI): calcd. for $C_{11}H_7Cl_2N_2$ 236.9986; found 236.9980.

2,4-Dichloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (39): NaH (60% in oil, 2.1 mmol) was added to a stirred 0.4 M suspension of 2,4-dichloro-9*H*-pyrido[2,3-*b*]indole (**38**) (1 equiv.) in DMF at 0 °C. After stirring at 0 °C for 20 min, EOMCl (2 equiv.) was added dropwise. The reaction mixture was stirred for 12 h and then poured into a 5% aqueous saturated $NaHCO_3$ solution and extracted with EtOAc (3×20 mL). The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 4:6) to afford compound **39** (246 mg, 80% yield) as a white solid; m.p. 111–113 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3107, 2980, 2911, 1574, 1549, 1468, 1388, 1311, 1119, 1076, 1062, 836, 750, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.36 (d, J = 7.9 Hz, 1 H), 7.63 (d, J = 8.1 Hz, 1 H), 7.56 (td, J = 8.2, 7.2, 1.1 Hz, 1 H), 7.36 (td, J = 8.2, 7.2, 1.1 Hz, 1 H), 7.18 (s, 1 H), 5.83 (s, 2 H), 3.52 (q, J = 6.9 Hz, 2 H), 1.15 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5 (C), 147.3 (C), 139.2 (2×C), 127.7 (CH), 122.9 (CH), 121.8 (CH), 119.6 (C), 116.2 (CH), 112.6 (C), 110.7 (CH), 71.3 (CH_2), 64.5 (CH_2), 15.0 (CH_3) ppm. MS (CI): m/z = 295 [M + H^+]. HRMS (CI): calcd. for $C_{14}H_{12}Cl_2N_2O$ 295.0402; found 295.0402.

9-(Ethoxymethyl)-2,4-bis(phenylethynyl)-9*H*-pyrido[2,3-*b*]indole (42): A Schlenk tube with stir bar was charged with [$Pd(Cl)_2(CH_3CN)_2$] (8 mg, 0.03 mmol, 0.08 equiv.), X-Phos (29 mg, 0.06 mmol, 0.16 equiv.), 2,4-dichloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (**39**; 100 mg, 0.34 mmol, 1 equiv.), and Cs_2CO_3 (577 mg, 1.77 mmol, 5.2 equiv.). The tube was evacuated and back-filled with argon (repeated for three additional times). Anhydrous acetonitrile (620 μL, 0.6 mmol/mL) was added (when degassed solvent was used) and then phenylacetylene (91 mg, 100 μL, 0.884 mmol, 2.6 equiv.) was injected and the reaction mixture was stirred overnight at 90 °C. After cooling to r.t., the products were extracted from the water layer with ethyl acetate, dried with $MgSO_4$, filtered through Celite and the solvents were removed under reduced pressure. The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 4:6) to afford **42** (91 mg, 62% yield) as a yellow solid; m.p. 65–67 °C (EtOH). IR (neat powder): $\tilde{\nu}$ = 3016, 2970, 2211, 1571, 1559, 1442, 1365, 1216, 1083, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, J = 7.7 Hz, 1 H), 7.73–7.64 (m, 5 H), 7.61 (s, 1 H), 7.58 (app. td, J = 1.1, 7.3, 8.1 Hz, 1 H), 7.48–7.45 (m, 3 H), 7.40–7.35 (m, 4 H), 5.93 (s, 2 H), 3.58 (q, J = 6.9 Hz, 2 H), 1.16 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9 (C), 140.3 (C), 138.5 (C), 132.2 (2×CH), 132.0 (2×CH), 129.5 (CH), 129.0 (CH), 128.8 (2×CH), 128.5 (2×CH), 127.9 (CH), 124.6 (C), 122.8 (CH), 122.7 (CH), 122.6 (C), 122.4 (C), 121.4 (CH), 120.8 (C), 115.4 (C), 110.6 (CH), 97.8 (C), 89.6 (C), 89.5 (C), 86.0 (C), 71.2 (CH_2), 64.4 (CH_2), 15.1 (CH_3) ppm. MS (ESI): m/z = 382 [M + H^+ – EtOH]$^+$, 427 [M + H^+].

4-Chloro-2-(2-cyclohexyleth-1-ynyl)-9-(ethoxymethyl)-9*H*-pyrido-[2,3-*b*]indole (43): Into a Schlenk tube with a screw cap, were intro-

duced under argon, 2,4-dichloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]-indole (**39**; 120 mg, 0.408 mmol, 1 equiv.), cyclohexylacetylene (135 μL, 1.02 mmol, 2.5 equiv.), $[PdCl_2(PPh_3)_2]$ (29 mg, 0.04 mmol, 0.1 equiv.), CuI (16 mg, 0.08 mmol, 0.2 equiv.), and PPh_3 (11 mg, 0.04 mmol, 0.1 equiv.), followed by addition of Et_3N (1.2 mL) and DMF (720 μL). The reaction mixture was stirred at 80 °C (the reaction was monitored by TLC). After 12 h of heating, the reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered through Celite and the solvents were evaporated to dryness. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 2:8) to afford compound **43** (109 mg, 73% yield) as a brown solid; m.p. 84–86 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3078, 2928, 2853, 2224, 1587, 1572, 1469, 1387, 1081, 1065, 831, 749 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.34 (d, J = 7.8 Hz, 1 H), 7.58 (d, J = 8.2 Hz, 1 H), 7.48 (td, J = 8.2, 7.2, 1.1 Hz, 1 H), 7.28 (td, J = 7.8, 1.1 Hz, 1 H), 7.18 (s, 1 H), 5.85 (s, 2 H), 3.44 (q, J = 6.9 Hz, 2 H), 2.60 (m, 1 H), 1.87 (br. s, 2 H), 1.72 (br. s, 2 H), 1.55 (br. s, 3 H), 1.33 (br. s, 3 H), 1.06 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3 (C), 139.9 (C), 139.8 (C), 137.8 (C), 127.8 (CH), 123.2 (CH), 121.5 (CH), 120.6 (CH), 120.0 (C), 113.3 (C), 110.7 (CH), 95.9 (C), 80.4 (C), 71.4 (CH_2), 64.4 (CH_2), 32.4 ($2\times CH_2$), 29.9 (CH), 25.9 (CH_2), 25.1 ($2\times CH_2$), 15.1 (CH_3) ppm. MS (CI): m/z = 367 [M + H^+]. HRMS (CI): calcd. for $C_{22}H_{24}ClN_2O$ 367.1577; found 367.1577.

4-Chloro-9-(ethoxymethyl)-2-(phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]-indole (44): Into a Schlenk tube with a screw cap, were introduced under argon, 2,4-dichloro-9-(ethoxymethyl)-9*H*-pyrido[2,3-*b*]indole (**39**; 50 mg, 0.17 mmol, 1 equiv.), phenylacetylene (66 μL, 0.51 mmol, 3 equiv.), $[PdCl_2(PPh_3)_2]$ (12 mg, 0.017 mmol, 0.1 equiv.), CuI (7 mg, 0.034 mmol, 0.2 equiv.), and PPh_3 (5 mg, 0.017 mmol, 0.1 equiv.), followed by Et_3N (600 μL) and DMF (300 μL). The reaction mixture was stirred at 80 °C (the reaction was monitored by TLC) and, after 12 h of heating, the reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered through Celite and the solvents were evaporated to dryness. The residue was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 3:7) to afford compound **44** (40 mg, 65% yield) as a brown solid; m.p. 162–164 °C (CH_2Cl_2/petroleum ether). IR (neat powder): $\tilde{\nu}$ = 3107, 2207, 1589, 1548, 1467, 1387, 1310, 1076, 1063, 837, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, J = 7.9 Hz, 1 H), 7.68 (d, J = 8.3 Hz, 1 H), 7.66–7.63 (m, 2 H), 7.59 (td, J = 8.3, 7.2, 1.1 Hz, 1 H), 7.48 (s, 1 H), 7.41–7.38 (m, 4 H), 5.96 (s, 2 H), 3.56 (q, J = 6.9 Hz, 2 H), 1.16 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4 (C), 140.0 (C), 139.2 (C), 137.8 (C), 132.2 ($2\times CH$), 129.2 (CH), 128.5 ($2\times CH$), 128.0 (CH), 123.3 (CH), 122.3 (C), 121.6 (CH), 120.7 (CH), 119.9 (C), 113.8 (C), 110.7 (CH), 89.8 (C), 89.1 (C), 71.4 (CH_2), 64.5 (CH_2), 15.1 (CH_3) ppm. MS (CI): m/z = 361 [M + H^+]. HRMS (CI): calcd. for $C_{22}H_{18}ClN_2O$ 361.1108; found 361.1108.

2-(2-Cyclohexyleth-1-ynyl)-9-(ethoxymethyl)-4-(4-methoxyphenyl)-9*H*-pyrido[2,3-*b*]indole (45): At r.t., under an inert atmosphere, a solution of $[Pd(PPh_3)_4]$ (31 mg, 0.026 mmol, 0.15 equiv.), 4-methoxyphenylboronic acid (40 mg, 0.26 mmol, 1.5 equiv.), and 0.3 M aqueous K_2CO_3 (72 mg, 0.52 mmol, 3 equiv.) were added to a suspension of **43** (50 mg, 0.172 mmol, 1 equiv.) in 1,4-dioxane (7.2 mL). The solution was stirred at 100 °C for 12 h then, after cooling to r.t., the solution was filtered through Celite and the solvents were removed under reduced pressure. The product was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 4:6) to afford **45** (54 mg, 71% yield) as a yellow oil. IR (NaCl): $\tilde{\nu}$ = 3068, 2927, 2852, 2226, 1609, 1577, 1558, 1510, 1465, 1293, 1246, 1174, 1082, 1029, 832, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.7 Hz, 1 H), 7.64 (d, J = 8.2 Hz, 1 H), 7.59 (d, J = 8.9 Hz, 2 H), 7.45 (ddd, J = 8.2, 7.1, 1.1 Hz, 1 H), 7.24 (s, 1 H), 7.09 (td, J = 7.1, 1.1 Hz, 1 H), 7.08 (d, J = 8.9 Hz, 2 H), 5.98 (s, 2 H), 3.92 (s, 3 H), 3.57 (q, J = 7.0 Hz, 2 H), 2.68 (m, 1 H), 1.96 (br. s, 2 H), 1.79 (br. s, 2 H), 1.60 (br. s, 4 H), 1.37 (br. s, 2 H), 1.16 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1 (C), 152.3 (C), 145.0 (C), 140.0 (C), 139.6 (C), 130.7 (C), 130.0 ($2\times CH$), 126.9 (CH), 122.5 (CH), 121.4 (CH), 120.7 (C), 120.5 (CH), 114.2 ($2\times CH$), 112.7 (C), 110.5 (CH), 94.7 (C), 81.5 (C), 71.1 (CH_2), 64.2 (CH_2), 55.4 (CH_3), 32.5 ($2\times CH_2$), 29.9 (CH), 25.9 (CH_2), 25.0 ($2\times CH_2$), 15.1 (CH_3) ppm. MS (ESI): m/z = 439.1 [M + H^+]. HRMS (ESI, 100 °C): calcd. for $C_{29}H_{30}N_2O_2$ 439.2389; found 439.2384.

9-(Ethoxymethyl)-4-(4-methylpiperazin-1-yl)-2-(phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (46): At r.t., 4-chloro-9-(ethoxymethyl)-2-(phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (**44**; 30 mg, 0.083 mmol, 1 equiv.) was dissolved in *N*-methylpiperazine (4 mL) in a microwave vial. The solution was stirred at 200 °C for 1 h under microwave irradiation (Biotage Initiator). The resulting mixture was quenched with water and then extracted with EtOAc. The resulting organic layers were dried with $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The product was purified by column chromatography on alumina (EtOAc) to afford compound **46** (30 mg, 84% yield) as a yellow solid; m.p. 55–58 °C (EtOH). IR (neat powder): $\tilde{\nu}$ = 3068, 2923, 2850, 1562, 1453, 1472, 1092, 1002, 736, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.7 Hz, 1 H), 7.68–7.64 (m, 3 H), 7.50 (td, J = 8.3, 1.1 Hz, 1 H), 7.40–7.35 (m, 3 H), 7.34 (td, J = 8.1, 1.1 Hz, 1 H), 7.06 (s, 1 H), 5.97 (s, 2 H), 3.56 (q, J = 6.9 Hz, 2 H), 3.42 (br. s, 4 H), 2.83 (br. s, 4 H), 2.50 (s, 3 H), 1.14 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8 (C), 153.5 (C), 140.1 (C), 139.2 (C), 132.2 ($2\times CH$), 128.9 (CH), 128.4 ($2\times CH$), 126.1 (CH), 123.0 (CH), 122.7 (C), 120.9 (CH), 120.2 (C), 110.4 (CH), 109.6 (CH), 107.3 (C), 90.3 (C), 88.5 (C), 71.2 (CH_2), 64.2 (CH_2), 55.2 ($2\times CH_2$), 50.4 ($2\times CH_2$), 46.3 (CH_3), 15.1 (CH_3) ppm. MS (CI, 200 °C): m/z = 425 [M + H^+]. HRMS (CI): calcd. for $C_{27}H_{28}N_4O$ 425.2341; found 425.2341.

2-(2-Cyclohexyleth-1-ynyl)-9-(ethoxymethyl)-2-(phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (47): Into a Schlenk tube fitted with a screw cap, were introduced under argon, 4-chloro-9-(ethoxymethyl)-2-(phenyleth-1-ynyl)-9*H*-pyrido[2,3-*b*]indole (**44**; 67 mg, 0.186 mmol, 1 equiv.), cyclohexylacetylene (60 mg, 0.558 mmol, 3 equiv.), $[PdCl_2(PPh_3)_2]$ (14 mg, 0.02 mmol, 0.1 equiv.), CuI (8 mg, 0.04 mmol, 0.2 equiv.), PPh_3 (2 mg, 0.02 mmol, 0.1 equiv.), then anhydrous Et_3N (600 μL) and anhydrous DMF (300 μL). The reaction mixture was stirred at 80 °C (the reaction was monitored by TLC) for 12 h, then poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered through Celite and the solvents were evaporated to dryness. The residue was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 3:7) to afford compound **47** (61 mg, 76% yield) as a brown oil. IR (NaCl): $\tilde{\nu}$ = 3056, 2927, 2852, 2218, 1573, 1559, 1466, 1447, 1348, 1291, 1217, 1092, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, J = 7.7 Hz, 1 H), 7.66 (d, J = 7.6 Hz, 1 H), 7.64–7.62 (m, 2 H), 7.55 (td, J = 7.3, 1.1 Hz, 1 H), 7.48 (s, 1 H), 7.39–7.32 (m, 4 H), 5.95 (s, 2 H), 3.54 (q, J = 6.9 Hz, 2 H), 2.83 (m, 1 H), 2.05 (br. s, 2 H), 1.85 (br. s, 2 H), 1.68 (br. s, 4 H), 1.44 (br. s, 2 H), 1.14 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.1 (C), 140.1 (C), 138.6 (C), 132.1 ($2\times CH$), 128.9 (CH), 128.5 ($2\times CH$), 127.7 (CH), 125.6 (C), 123.2

(CH), 122.7 (C), 122.5 (CH), 121.1 (CH), 121.0 (C), 115.5 (C), 110.5 (CH), 104.0 (C), 89.7 (C), 89.2 (C), 77.9 (C), 71.1 (CH_2), 64.3 (CH_2), 32.6 ($2\times CH_2$), 30.3 (CH), 25.9 (CH_2), 25.1 ($2\times CH_2$), 14.9 (CH_3) ppm. MS (CI): m/z = 433 [M + H^+].

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all new compounds are available.

Acknowledgments

The authors would like to thank the French Ministère de l'Enseignement Supérieur et de la Recherche (MESR) for a graduate fellowship (to C. S.) and the European Union (contract number LSHB-CT-2004-503467) for financial support.

[1] a) D. Bolton, I. T. Forbes, C. J. Hayward, D. C. Piper, D. R. Thomas, M. Thompson, N. Upton, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1941–1946; b) B. E. Love, *Top. Heterocycl. Chem.* **2006**, *2*, 93–128.

[2] C. Moquin-Pattey, M. Guyot, *Tetrahedron* **1989**, *45*, 3445–3450.

[3] J. S. Kim, K. Shinya, K. Furihata, H. Hayakawa, H. Seto, *Tetrahedron Lett.* **1997**, *38*, 3431–3434.

[4] For recent references, see: a) B. Joseph, L. Meijer, F. Liger, Patent, FR 28976377, **2006**; *Chem. Abstr.* **2006**, *144*, 390900; b) P. Sennhenn, A. Mantoulidis, M. Treu, U. Tontsch-Grunt, W. Spevak, D. McConnell, A. Schoop, R. Brueckner, A. Jacobi, U. Guertler, G. Schnapp, C. Klein, F. Himmelsbach, A. Pautsch, B. Betzemeier, L. Herfurth, J. Mack, D. Wiedenmayer, G. Bader, U. Reiser, Appl. Int. WO **2006**/131552, **2006**; *Chem. Abstr.* **2006**, *146*, 62695; c) M. E. Hepperle, J. F. Liu, R. S. Rowland, D. Vitharana, Appl. Int. WO **2007**/097981, **2007**; *Chem. Abstr.* **2007**, *147*, 322959; d) S. Das, J. W. Brown, Q. Dong, X. Gong, S. W. Kaldor, Y. Liu, B. R. Paraselli, N. Scorah, J. A. Stafford, M. B. Wallace, Appl. Int. WO **2007**/044779, **2007**; *Chem. Abstr.* **2007**, *146*, 441771; e) G. L. Wisler, Appl. Int. WO **2008**/079398, **2008**; *Chem. Abstr.* **2008**, *149*, 119648; f) J. W. Brown, Q. Dong, B. R. Paraselli, J. A. Stafford, M. B. Wallace, H. Wijesekera, Appl. Int. WO **2008**/054956, **2008**; *Chem. Abstr.* **2008**, *148*, 495928; g) J. W. Brown, Q. Dong, B. R. Paraselli, J. A. Stafford, M. B. Wallace, H. Wijesekera, Appl. Int. WO **2008**/045834, **2008**; *Chem. Abstr.* **2008**, *148*, 472012.

[5] For recent references, see: a) A. V. Sadovoy, G. A. Golubeva, *Chem. Heterocycl. Compd.* **2005**, *41*, 1267–1272; b) K. Tanaka, M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1659–1664; c) C. Bonini, M. Funicello, P. Spagnolo, *Synlett* **2006**, 1574–1576; d) N. Koichi, K. Mitsuru, *Arkivoc* **2006**, 245–260; e) P. Vera-Luque, R. Alajarin, J. Alvarez-Builla, J. J. Vaquero, *Org. Lett.* **2006**, *8*, 415–418; f) D. J. St. Jean, S. F. Poon, J. L. Schwarzbach, *Org. Lett.* **2007**, *9*, 4893–4896; g) M. Pudlo, D. Csányi, F. Moreau, G. Hajós, Z. Riedl, J. Sapi, *Tetrahedron* **2007**, *63*, 10320–10329; h) M. Panunzio, E. Tamanini, Y. St-Denis, F. M. Sabbatini, R. D. Fabio, Z. Xia, *Synth. Commun.* **2007**, *37*, 4239–4244; i) C. Schneider, D. Gueyrard, F. Popowycz, B. Joseph, P. G. Goekjian, *Synlett* **2007**, 2237–2241; j) V. Iaroshenko, U. Groth, N. Kryvokhyzha, S. Obeid, A. Tolmachev, T. Wesch, *Synlett* **2008**, 343–346.

[6] a) E. Erba, M. L. Gelmi, D. Pocar, *Tetrahedron* **2000**, *56*, 9991–9997; b) Y.-L. Chen, H.-M. Hung, C.-M. Lu, K.-C. Li, C.-C. Tzeng, *Bioorg. Med. Chem.* **2004**, *12*, 6539–6546; c) C. Willemann, R. Grünert, P. J. Bednarski, R. Troschütz, *Bioorg. Med. Chem.* **2009**, *17*, 4406–4419.

[7] I. El Sayed, P. Van der Veken, K. Steert, L. Ghooghe, S. Hostyn, G. Van Baelen, G. Lemière, B. U. W. Maes, P. Cos, L. Maes, J. Joossens, A. Haemers, L. Pieters, K. Augustyns, *J. Med. Chem.* **2009**, *52*, 2979–2988.

[8] a) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; b) A. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *218–222*, 131–209; c) D. Prim, J.-M. Campagne, D. Joseph, B. Andrioletti, *Tetrahedron* **2002**, *58*, 2041–2075; d) J. P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710.

[9] a) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874–922; b) A. Soheili, J. Albaneze-Walker, J. A. Murry, P. G. Dormer, D. L. Hughes, *Org. Lett.* **2003**, *5*, 4191–4194; c) T. Ljungdahl, T. Bennur, A. Dallas, H. Emtenas, J. Martenson, *Organometallics* **2008**, *27*, 2490–2498.

[10] C. Schneider, D. Gueyrard, B. Joseph, P. G. Goekjian, *Tetrahedron* **2009**, *65*, 5427–5437.

[11] a) A. R. Katritzky, X. Lan, J. Z. Yang, O. V. Denisko, *Chem. Rev.* **1998**, *98*, 409–548; b) L. K. Mehta, J. Parrick, F. Payne, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1261–1267; c) A. A. Semenov, V. V. Tolstikhina, *Chem. Heterocycl. Compd.* **1984**, *20*, 345–355.

[12] a) A. L'Heureux, C. Thibault, R. Ruel, *Tetrahedron Lett.* **2004**, *45*, 2317–2319; b) C. Thibault, A. L'Heureux, R. S. Bhide, R. Ruel, *Org. Lett.* **2003**, *5*, 5023–5025; c) J. Elks, G. B. Webb, G. J. Gordon, J. D. Cocker, Patent GB 1268773; *Chem. Abstr.* **1970**, *72*, 43636 and *Chem. Abstr.* **1972**, *77*, 140760.

[13] a) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655; b) K. S. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 6523–6527.

[14] M. Thutewohl, H. Schirok, S. Bennabi, S. Figueroa-Pérez, *Synthesis* **2006**, 629–632.

[15] J. E. Backvall, E. E. Bjorkman, L. Pettersson, P. Siegbahn, *J. Am. Chem. Soc.* **1984**, *106*, 4369–4373.

[16] D. Gelman, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2003**, *42*, 5993–5996.

[17] Although we did not identify it here, in principle, there is no reason to believe that the Buchwald–Hartwig coupling could not similarly be used as the first step of the sequential double coupling reaction. For references on regioselective Sonogashira reactions on 2,4-dichloro-substituted heterocycles, see: a) M. H. Norman, N. Chen, Z. Chen, C. Fotsch, C. Hale, N. Han, R. Hurt, T. Jenkins, J. Kincaid, L. Liu, Y. Lu, O. Moreno, J. V. Santora, J. D. Sonnenberg, W. Karbon, *J. Med. Chem.* **2000**, *43*, 4288–4312; b) E. A. Reddy, D. K. Barange, A. Islam, K. Mukkanti, M. Pal, *Tetrahedron* **2008**, *64*, 7143–7150; c) A. M. Palmer, G. Muench, C. Brehm, P. J. Zimmermann, W. Buhr, M. P. Feth, W. A. Simon, *Bioorg. Med. Chem.* **2008**, *16*, 1511–1530.

[18] B. Witulski, J. R. Azcon, C. Alayrac, A. Arnautu, V. Collot, S. Rault, *Synthesis* **2005**, 771–780.

[19] J. Elks, G. I. Gregory, J. D. Cocker, L. Stephenson, W. K. Warburton, patent GB 1268772; *Chem. Abstr.* **1970**, *72*, 111444.

Received: June 2, 2010
Published Online: October 20, 2010

